Is comprehensive medication review cost-effective for patients admitted to hospital?

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ABSTRACT

Problematic polypharmacy is a major public health problem, linked to high morbidity, mortality and use of National Health Service (NHS) resources. Medicines optimisation supports management of polypharmacy, chronic conditions and comorbidities by ensuring appropriate use of medicines.

A key component is comprehensive medication review (CMR) – evaluating patients' medication to optimise use and reduce medication-related problems and waste. CMR is recommended for problematic polypharmacy but its cost-effectiveness in UK hospitals is unknown and uptake is low. This thesis investigates CMR cost-effectiveness in UK NHS hospitals.

CMR is complex, with multiple interacting components, and economic evaluation should accommodate the context and complexity.

Two de novo cost-effectiveness models were developed, which demonstrated that CMR compared to usual care is a cost-effective use of resources for the general population of elderly acutely hospitalised patients over a short timeframe and for elderly patients with heart failure over a long timeframe.

Analysis of data from 3,043 patients in five London hospitals revealed the difference between the number of medicines on discharge and the number of medicines on admission was less with CMR than with usual care. CMR was associated with an increase in the number of medicines deprescribed, held and started. The saving from deprescribing medicines was -£2.78 per month per patient larger in the CMR group than in the usual care group. The results of the empirical study complement the findings from both cost-effectiveness models.

Further review and analysis showed that targeting CMR at patients with significant morbidity and mortality, potentially inappropriate prescribing and high treatment costs may increase its health and economic impact. This was exemplified by the cost-effectiveness of CMR for patients with heart failure; the study could be replicated for other diseases. This thesis indicates that well-delivered CMR should be routine hospital care for older patients with co-morbidity and/or specific target conditions.

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ABBREVIATIONS

A&E	Accident and emergency
ACE inhibitors	Angiotensin-converting enzyme inhibitors
ACEIs	Angiotensin-converting enzyme inhibitors
ADE	Adverse drug event
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse drug reactions
AHRQ	Agency for Healthcare Research and Quality
AOU	Assessment of underutilization index
ARBs	Angiotensin II receptor blockers
BNF	British National Formulary
BOLD	Burden of Obstructive Lung Disease
CBA	Cost-benefit analysis
CCA	Cost-consequences analysis
CCG	Clinical commissioning group
CCS	Clinical Classification System
CEA	Cost-effectiveness analysis
CI	Confidence interval
CLAHRC NWL	Collaboration for Leadership in Applied Health Research and Care Northwest London
CMA	Cost-minimisation analysis
CMR	Comprehensive medication review
COPD	Chronic obstructive pulmonary disease
COX-1 and COX-2	Cyclo-oxygenase-1 and 2
CPRD	Clinical Practice Research Datalink
CUA	Cost-utility analysis
CWH	Chelsea and Westminster Hospital NHS Foundation Trust
df	Degrees of freedom
DSA	Deterministic sensitivity analysis
DSUM	Discharge summaries
ED	Emergency department
EDSS	Expanded Disability Status Scale

EORTC-8D	European Organization of Randomized Controlled Trials 8 Dimension
EUnetHTA	European Network for Health Technology Assessment
EUR	Euro
EuroQoL, EQ-5D	European Quality of Life, Five Dimensions questionnaire
Foundation Year 1/2	FY1/2
GBP	Pound sterling
GEM	Geriatric evaluation and management
GP	General practitioner
HCUP	Healthcare Cost and Utilization Project
HES	Hospital Episode Statistics
HF	Heart failure
HIC	High-income countries
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
HUI3	Health Utilities Index Mark 3
ICD-10	International Classification of Diseases, Revision 10
ICER	Incremental cost-effectiveness ratio
IDU	Inappropriate drug use
IHE	Institute of Health Economics
IMR	Interim medication review
IMU	Inappropriate medication use
IP	Inappropriate prescribing
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
LMIC	Low and middle-income countries
LOS	Length of stay
MAI	Medication appropriateness index
Md	Median
ME	Medication errors

mg	Milligram
ml	Millilitre
MRA	Mineralocorticoid receptor antagonist
MRC	Medical Research Council
MUR	Medicines use review
MWP	Maximum willingness to pay
NE	North east
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPs	Natriuretic peptides
NSAIDs	Non-steroidal anti-inflammatory drugs
NW	North west
NWL	North West London
NYHA	New York Heart Association
ONS	Office for National Statistics
OR	Odds ratio
OTC	Over-the-counter
PCNE	Pharmaceutical Care Network Europe
PCPH	Primary Care and Public Health
PICO	Population, Intervention, Comparator, Outcome
PIM	Potentially inappropriate medication
PIMHF	Potentially Inappropriate Medicines in Heart Failure
PIP	Potentially inappropriate prescribing
PPI	Proton pump inhibitor
PSA	Probabilistic sensitivity analysis
PSS	Personal and social services
PSSRU	Personal Social Services Research Unit
PTSD	Post-traumatic stress disorder
Q1 and Q3	First and third quartile
QALY	Quality-adjusted life year
QI	Quality improvement
RCT	Randomised control trial

ReMAC	Review of Medicines in Acute Care
RR	Relative risk
SALT	Study of Ascending Levels of Tolvaptan in Hyponatremia
SD	Standard deviation
SDD	Standard daily dose
SE	Standard error
SE	South east
SF-36	Short Form (36) Health Survey
SF-6D	Short-Form Six-Dimension
SGPMCG	The Scottish Government Polypharmacy Model of Care Group
SHIFT-Evidence	Successful Healthcare Improvements From Translating Evidence in complex systems
SHMI	Summary Hospital-level Mortality Indicator
Sig.	significance (p-value)
SPC	Statistical process control
SSRIs	Selective serotonin reuptake inhibitors
START	Screening Tool to Alert doctors to Right Treatment
STD	Sexually transmitted disease
Std.	Standard
STOPP	Screening Tool of Older Person's Prescriptions
SW	South west
t	t-value
TB	Tuberculosis
UC	Usual care
USD	United States dollar
VAT	Value added tax
WMD	Weighted mean difference
$\bar{x}$	Mean
µg	Microgram

LIST OF EQUATIONS

CHAPTER 1 INTRODUCTION

The use of prescribed medication in the United Kingdom and internationally is increasing (IMS, 2015; NICE, 2015a). This is in part related to better treatments being available on the market. However, as patients have more complex needs it is important to ensure that the medicines are taken appropriately and that they provide more benefit than harm.

Optimising an individual's medicines is increasingly necessary to maximise benefits and is a crucial part of pharmaceutical care for people with comorbidities and long-term conditions and those on polypharmacy. Medicines optimisation is a term used to describe 'a person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines' (NICE, 2015a). An important component of medicines optimisation is medication review.

Medication review is an intervention that can optimise medicines use, detect drug-related problems and reduce problematic polypharmacy (Griese *et al*., 2018; Pharmaceutical Care Network Europe, 2016). A comprehensive medication review (CMR), also called structured or advanced review, is a medication review done systematically with adequate information about the patient and with the patient's involvement. It often uses structured criteria for detecting potentially inappropriate prescribing (PIP). The National Health Service (NHS) has limited resources and it is therefore essential to determine the cost-effectiveness of CMR.

The purpose of the introductory chapter is to set out the background and highlight the most important literature concerning CMR and its economic impact on the NHS. Firstly, I discuss the impact of comorbidity in general and the subsequent polypharmacy on patients and the wider healthcare system. Secondly, I explore the potential solutions for improving problematic polypharmacy for patients, by conducting medication reviews. I present the classification and the evidence around the effectiveness of medication reviews. Thirdly, I discuss the development in costs and consumption of medicines internationally and in the UK. I present the methods for conducting economic evaluations in healthcare and outline the existing literature relating to the economic impact of CMR. Fourthly, I present the current gaps in the literature about cost-effectiveness of CMR and critique the currently available

evidence. The importance of conducting research in this area and the rationale for this thesis are discussed and the aims and research question developed to address the gaps in the literature are formed. Finally, the structure of the thesis and chapter outline are presented.

1.1 Polypharmacy and comorbidities

Approximately 15 million people in England are living with long-term conditions. This number is projected to increase to 18 million by 2025 (House of Commons Health Committee, 2014). Importantly, many patients have two or more long-term conditions and this coexistence is usually described as comorbidity. The number of patients with comorbidities is increasing and was estimated to be 2.9 million in 2018 (Department of Health/Long Term Conditions, 2012). The financial impact of long-term conditions on the NHS is estimated at £138.18 billion, suggesting that the treatment of the 30% of the population with long-term conditions is associated with 70% of total healthcare expenditure, including medicines (Department of Health/Long Term Conditions, 2012; ONS, 2019). People with comorbidities contribute to the increased demand on health services and are more frequently the subjects of polypharmacy because treatment of multiple conditions often requires several medicines and results in polypharmacy (NICE, 2014).

Polypharmacy, the concurrent use of multiple medication items by one individual, is driven by evidence-based treatment to modify disease and to prevent future morbidity and mortality (Duerden, Avery & Payne, 2013). However, as life expectancy reduces, the case for using such drugs weakens. With each additional drug, the relative impact of preventive medicines is reduced (NICE, 2014). While appropriate polypharmacy can be beneficial to patients, polypharmacy which has not been optimised may be harmful.

Problematic polypharmacy is a major public health problem and it is linked to high mortality and considerable use of NHS hospital resources. Problematic polypharmacy is linked with potentially inappropriate prescribing (Fialová *et al*., 2005) and adverse drug reactions (ADR) (Davies *et al*., 2009). Severe adverse drug events account for 5-17% of hospital admissions for older patients (Duerden *et al*., 2013). People admitted to hospital because of ADR are at greater risk of in-hospital

mortality, with figures suggesting that 5% of ADR admissions result in mortality (Wu *et al*., 2010). ADR are also responsible for 20% of readmissions to hospital within one year of discharge (Davies, Green, Mottram, Rowe & Pirmohamed, 2010). The National Institute for Health and Care Excellence (NICE) estimated that a reduction in admissions due to avoidable ADR could save the NHS up to £530 million/per year (NICE, 2015b).

1.2 Medication review

Medication review is defined in number of ways. However, the two most common definitions are similar. The first was introduced in the Guide to Medication Review (Room for Review, 2002). This document defined medication review as "a structured, critical examination of a person's medicines with the objective of reaching an agreement with the person about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste." The second common definition was developed by a panel of European experts from Pharmaceutical Care Network Europe (PCNE) who defined a medication review as "an evaluation of all the patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug related problems and recommending interventions." (Griese *et al*., 2018).

In the guidelines on medicines optimisation (NICE, 2015a), NICE recommends conducting CMR for people with indication for a review. This includes older patients, patients with polypharmacy and patients with chronic or long-term conditions. The appropriately conducted CMR should consider the patient's and carers' views about medicines, including any concerns, problems and understanding. The person delivering CMR should examine all the patients' medicines including prescribed medicines, over-the-counter (OTC) medicines and complementary medicines. The reviewer should consider the safety, effectiveness and appropriateness of medicines for a given patient. The reviewer should also check whether the use of these medicines is recommended by the national guidance. CMR should also consist of checking whether a patient has any risk factors that can lead to ADR and whether the patient requires any monitoring (NICE, 2015a).

1.2.1 Types of medication review

Medication review is an umbrella term that encompasses different types of interventions. Medication review can be therefore classified differently depending on the purpose of the review, type of sources of information available to the person delivering the review, the setting in which it is delivered and the type of healthcare professional delivering the intervention.

1.2.1.1 Purpose of the intervention

Medication review can be classified into three levels based on the purpose of the medication review:

Level 1: Prescription review

The purpose of the review is to address technical issues with the prescription (anomalies, cost-effectiveness, changed items etc.) (Clyne, Blenkinsopp & Seal, 2008). The patient does not need to be present during a prescription review, however the patient or carer should be consulted about any changes to the medicine's regime (Clyne *et al*., 2008; Latif, Boardman & Pollock, 2013; NICE, 2015a; Room for Review, 2002). This level of review is usually conducted by a single healthcare professional and does not always include full medical notes of the patient. The review only considers prescription medication and not OTCs and complementary medicines. The review is focused on the medicines and does not include reviewing the medical condition of patients and the appropriateness of the medical regime for that condition (Bulajeva *et al*., 2014; Clyne *et al*., 2008; Latif *et al*., 2013; NICE, 2015a; Room for Review, 2002).

An example of level 1 review is medicines use review (MUR), an intervention done by community pharmacists that aims to improve patients' knowledge and use of medicines (NICE, 2015a). However, there is discrepancy in the literature, as some sources classify MUR as a level 2 review (Bulajeva *et al*., 2014; Clyne *et al*., 2008).

Level 2: Concordance and compliance review

The purpose of the level 2 review is to consider the patient's behaviour and compliance with the medicine's regime. Usually the patient is present during the

review and if there are any changes the patient must be present. Literature is ambiguous about what criteria qualify a medication review as a level 2 review. Some authors argue that the healthcare professional having access to the patient's notes is an essential part of a level 2 review (NICE, 2015a). Other sources describe MUR (where the pharmacist does not have access to the notes) as an example of a level 2 review and mention that access to the notes is possible in a level 2 review, but not essential (Bulajeva *et al*., 2014; Clyne *et al*., 2008).

The review includes all medicines including prescription, OTC and complementary medicines. Examples of such reviews are review of medicines for a certain condition such as asthma (Bulajeva *et al*., 2014; Clyne *et al*., 2008; Latif *et al*., 2013; NICE, 2015a; Room for Review, 2002).

Level 3: Clinical medication review

The purpose of a level 3 review is to review the use of medicines in the context of the patient's condition. The reviewer considers all the patient's medicines including prescription, OTC and complementary medicines, and also considers the condition and lifestyle of the patient. A clinical medication review requires the healthcare professional to have access to the patient's notes and medicines records and the patient is present during the review. Therefore, this level of review is the most compliant with the principles of patient involvement/engagement. The review can be conducted by a single health professional or a multidisciplinary team. An example of clinical medication review is comprehensive medication review (CMR) (Bulajeva *et al*., 2014; Clyne *et al*., 2008; Latif *et al*., 2013; NICE, 2015a; Room for Review, 2002).

Some of the literature also describes level 0 medication review, which is an ad hoc review. It is described as an unplanned, opportunistic and unstructured review, where either a healthcare professional or patient are not required to be involved. Examples of such reviews include a question from a receptionist at a GP surgery to a patient about medicines or ad hoc discussion between clinicians about the medicines of a patient. This level of review of medicines does not meet the requirements of a medication review set by the NICE definition, however it is a

medication review in accordance with the PCNE definition (Griese *et al*., 2018; NICE, 2015a; Room for Review, 2002).

1.2.1.2 Type and source of available information for the reviewer about the patient

The PCNE classifies medication review according to how advanced it can be, based on what sources of information are available for the healthcare professional during the review (Griese *et al*., 2018).

Simple medication review (type 1)

A simple medication review can be based on whatever information is available to the healthcare professional conducting the review. The review is aimed at detection of adverse effects, drug interactions, dosage problems and adherence problems.

Intermediate medication review (type 2A and 2B)

Type 2A – the review is based on information from the medical history and directly from the patient or carer. The review may reveal interactions of medicines with food and self-prescribed OTC medicines, problems with effectiveness of medicines and additional adverse effects that the patient currently experiences.

Type 2B – includes both the medical history of the patient and other medical information (for example, data from the GP practice). A type 2B medication review can identify if a medicine is prescribed without an indication or if a patient is missing a prescription for an already-identified indication.

Advanced medication review (type 3)

An advanced medication review includes all three forms of information: patient information, medical history and clinical information available from other sources. The review is a combination of medication review types 1, 2A and 2B and therefore aims to identify all the problems with medicines.

1.2.1.3 Setting in which medication review is delivered (inpatient hospital settings)

Medication review can be delivered in various settings: primary care, community care, care homes and both outpatient and inpatient secondary care. There is limited research evaluating the economic impact of medication review delivered in an inpatient hospital setting and currently to my knowledge there are no studies in the literature which look at cost-effectiveness of medication review done in UK hospitals. At the same time, the NHS's spending on hospital prescribing is increasing significantly and in the financial year 2017/18 it was higher than primary care prescribing for the first time (NHS Digital, 2018c). More information is available in section 1.3.1 'Medicines use and costs' of this chapter.

Therefore, to address the gap in the literature, this PhD focuses solely on medication review delivered within secondary care for inpatients. For this reason, only the types of medication review delivered in secondary care are described in this section.

Medication review in hospitals can occur at any point during the patient's stay at the hospital. Prior to a medication review taking place, the process of medicines reconciliation should occur, during which a trained clinical pharmacist should conduct initial screening of medicines, to ensure that their medicines are clinically appropriate (Szymanski, Marvin, Ward & Jubraj, 2016; Ward *et al*., 2019).

In hospitals medication review can be classified as an interim medication review (IMR) or a comprehensive medication review (CMR).

The IMR can be undertaken when a patient first appears in an acute state or when the patient's condition deteriorates or improves. The main purpose of the IMR is the immediate safety and wellbeing of the patient. During an IMR medicines could be withheld pending a later CMR (Szymanski *et al*., 2016; Ward *et al*., 2019).

A CMR is a 'structured critical examination of all current medication with the objective of reaching an agreement with the patient about treatment. The reviewer systematically considers the merits and risks of different medications, stops inappropriate medicines and starts others, optimising their impact, minimising the number of medication related problems and reducing waste' (Szymanski *et al*., 2016; Ward *et al*., 2019). CMR is distinct from routine review of drug charts by a

pharmacist during ward visits (The Healthcare Commission, 2007). The reviewer can be any healthcare professional who is recognised as capable of conducting a review and could be part of a full multidisciplinary team assessment. 'Deprescribing', permanently stopping medicines that are no longer appropriate or necessary, should be considered when completing a CMR (Jubraj *et al*., 2015). Before 'deprescribing' the reviewer should consider the patient's physical functioning, other medicines, comorbidities, preferences and lifestyles (Szymanski *et al*., 2016; Ward *et al*., 2019).

1.2.1.4 Healthcare professional delivering the intervention

At present there is no consensus on the type of healthcare professional most appropriate to conduct a medication review. Therefore, the review can be conducted by clinical pharmacists (e.g. pharmacist-led CMR), community pharmacists (e.g. MUR), general practitioners, physicians in nursing homes, hospital physicians (including all levels of consultants, senior doctors, junior doctors), nurses, pharmacy support technicians and practically any other healthcare professional capable of delivering a medication review. Medication review can also be delivered by a multidisciplinary team (NICE, 2015a; Room for Review, 2002).

NICE recommends that the appropriate healthcare professional to deliver CMR should be determined locally. The healthcare professional should have the knowledge and skills to deliver a review. That includes technical knowledge of medicines management, knowledge of therapeutic use of medicines and appropriate communication skills to engage the patient in the discussion about medicines (NICE, 2015a).

1.2.1.5 Medication review analysed in the PhD thesis

The PhD focuses on comprehensive medicines review (CMR) conducted for inpatients in the hospital setting and long-term care. Therefore, in the PhD thesis please refer to the CMR definition described in section 1.2.1.3 'Setting in which medication review is delivered (inpatient hospital settings)' of this chapter. The analysis conducted as part of the PhD looked at different healthcare professionals delivering CMR, however a major part of the analysis refers to CMR conducted by a hospital pharmacist. In the following chapters if it is not directly stated in the text that

it is another healthcare professional delivering CMR, then the text refers to a pharmacist-led CMR.

1.2.2 Effectiveness of medication review

In the guideline on medicines optimisation, NICE identified eight systematic literature reviews (Alldred *et al*., 2013; Christensen & Lundh, 2013; Hadi, Alldred, Briggs, Munyombwe & Closs, 2014; Holland *et al*., 2007; Kaboli, Hoth, McClimon & Schnipper, 2006; Patterson, Hughes, Kerse, Cardwell & Bradley, 2012; Rollason & Vogt, 2003; Ryan *et al*., 2011b) that studied the effectiveness of medication review or of other pharmacists' interventions that included medication review (NICE, 2015a).

Using the same search criteria as NICE, I identified 10 additional new systematic literature reviews published after the NICE guidelines or not included in the original guideline (Graabaek & Kjeldsen, 2013; Hatah, Braund, Tordoff & Duffull, 2013; Hill-Taylor *et al*., 2016; Hohl *et al*., 2015; Huiskes, Burger, van den Ende & van den Bemt, 2017; Jokanovic *et al*., 2015; Loh, Cheen & Wee, 2016; Meid, Lampert, Burnett, Seidling & Haefeli, 2015; Tesfaye, Castelino, Wimmer, Tabish & Zaidi, 2017; Thomas *et al*., 2014). I also identified three systematic literature reviews which were included in the NICE guidance, but had been updated since (Alldred, Kennedy, Hughes, Chen & Miller, 2016; Christensen & Lundh, 2016; Patterson *et al*., 2014).

Only six out of the total 21 identified studies looked at medication review conducted exclusively within a hospital or long-term care setting.

- (Christensen & Lundh, 2013, 2016)**:** The Cochrane systematic literature review with meta-analysis and the subsequent update included 10 randomised controlled trials (RCTs). The review compared CMR against usual care or other noncomprehensive medication review. The authors suggest that it is uncertain whether medication review reduces mortality and hospital readmission, however evidence was identified that medication review may reduce emergency department contacts. The authors concluded that due to short follow-up in the studies (ranging from 30 days to one year), there could be significant treatment effects that had been overlooked. To explore the effectiveness of medication review there is a need for high quality trials with long follow-up (at least one year) to give sufficient time for clinical

outcomes such as mortality, adverse drug events and hospital readmissions to occur.

- (Hill-Taylor *et al*., 2016)**:** Four RCTs were included, which looked at effectiveness of CMR using STOPP/START compared with usual care. The authors conclude that CMR using STOPP/START criteria can be effective in improving prescribing quality, humanistic, clinical and economic outcomes. In all four studies the rate of potentially inappropriate prescribing (PIP) was reduced.

  Meta-analysis was conducted to estimate the pooled treatment effect of CMR, which resulted in an estimated odds ratio of 2.98 (95% CI 1.30; 6.83) in favour of the CMR group. However, because of different implementation strategies of CMR across different local settings there was substantial heterogeneity in the results.

- (Hohl *et al*., 2015)**:** There were seven studies included – five RCTs and two controlled trials without randomisation. The studies were conducted on hospital wards, but none of them included the emergency department. The review did not find an effect of pharmacist-led medication review on patient outcomes, however the authors conclude that wide confidence intervals in outcomes such as mortality OR = 1.09 (95% CI 0.69; 1.72), length of hospital admission WMD[1] = -0.04 days (95% CI -1.63; 1.55) or hospital readmissions OR = 1.15 (95% CI 0.81; 1.63) indicate that the current evidence is insufficient to draw any meaningful conclusions. The authors suggest that additional research is required to influence the effect size of estimates and evaluate the effectiveness of CMR.

- (Graabaek & Kjeldsen, 2013)**:** The review included 31 studies; 21 were descriptive studies and 10 were controlled trials, of which six were RCTs. The review concluded that well implemented clinical pharmacist services have a positive effect on medication use, costs, health service use and drug-related readmissions. There was no statistically significant effect of CMR on mortality. There were also three studies with no statistically significant effect of CMR on

[1] Weighted mean difference.

readmissions and one study which reported a statistically significant impact of CMR on reduction in readmissions. The authors conclude that there was insufficient effect size in the study due to low sample size and low acceptance of pharmacists' recommendations. Moreover, the follow-up in the studies could have been too short to identify any meaningful effects of CMR on mortality and readmissions.

- (Kaboli *et al*., 2006)**:** The study combined evidence about CMR with other pharmaceutical care services such as medicines reconciliation, drug-class specific service and pharmacist participation on ward rounds. The review included 36 studies, of which 11 focused on medication review and medicines reconciliation. The addition of pharmacist service to care for inpatients improved patient care: seven of 12 studies that looked at adverse drug events (ADEs) as an outcome reported a reduction in ADE. Seven of 11 studies which focused on medication review reported improvement in appropriateness of medicines, adherence to treatment and knowledge about medicines. None of the studies reported worse clinical outcomes following a pharmacist intervention.

1.2.3 Complexity of medication review

The current evidence about medication review uses traditional methods to evaluate effectiveness and cost-effectiveness of CMR. In the PhD I present arguments as to why CMR should be considered a complex intervention and how this influences its evaluation.

Complex interventions have been defined by the Medical Research Council (MRC) as interventions containing several interacting components (Craig *et al*., 2006, 2018; MRC, 2000). The complexity of the intervention depends on the number and difficulty of behavioural factors associated with delivering the intervention as well as the number and variation of outcomes that the intervention may deliver. The complexity also depends on the number of target groups for which the intervention is delivered and the possibility of tailoring the intervention (Husereau *et al*., 2014).

Medication review fits the definition of complex intervention as it consists of several elements, which can all impact on the success or failure of the intervention.

Medication review is heavily influenced by behavioural factors relating both to the healthcare professionals delivering the intervention and to the patients. There is also variability in how the intervention is delivered and tailored to local needs. Medication review can be delivered to a broad target population and impacts on multiple possible outcomes (Christensen & Lundh, 2013, 2016; Graabaek, Bonnerup, Kjeldsen, Rossing & Pottegard, 2015; Graabaek & Kjeldsen, 2013; Hill-Taylor *et al*., 2016; Hohl *et al*., 2015; Lennox, Stillman, Barber & Reed, 2019; NICE, 2015a). In chapter 2, I provide an extensive overview of why medication review should be considered a complex intervention. The overview is based on the literature around evaluation of complex interventions and literature about evaluation of medication review.

Evaluating complex interventions can require more elaborate research methods as the evaluation may concentrate not only on establishing whether interventions work, but also on understanding how they work. Exploring the mechanisms of change can be as important as the final outcome of the complex intervention (Byng, Norman, Redfern & Jones, 2008; Oliveira, 2014). However, a lot of evaluations tend to treat interventions as 'black boxes', focusing mostly on the outcome and not on the mechanism for achieving the outcome (Anderson, 2008; Oliveira, 2014).

The health economic evaluation of complex interventions can be challenging, as the methods used in health technology assessment (HTA) do not always capture the wealth of effects of complex interventions (Oliveira, 2014). In section 1.3.2.4, I provide the most common challenges of economic evaluation of complex interventions and how researchers try to address them.

1.3 Health economics and medication review

1.3.1 Medicines use and costs

Projections from IQVIA (one of the largest companies that collects and analyses data about the use of medicines in the world; formerly known as Quintiles IMS) suggest that the total use of medicines worldwide will reach 4.5 trillion doses in 2020, which is an increase of 24% from 2015. This increase is mainly driven by low-income and middle-income countries (LMIC), where the biggest increase can be seen in China,

Indonesia, Brazil, India and African countries. The largest volume of medicines used are generics and non-original branded medicines, especially in the LMIC. The use of new medicines which were created in the last 10 years is projected to be 0.1% of all medicines use in these countries (IMS, 2015).

In high-income countries (HIC) the consumption of medicines is much more stable. However, the use of medicines still increases, with projections suggesting that in 2020 in Europe the number of doses used will increase to 916 billion doses from 818 billion in 2015. This increase is mainly driven by consumption of medicines in countries from central and eastern Europe such as Poland. The use of original branded and specialty medicines is higher in HIC compared to LMIC. The use of new medicines is projected to be 2-3% of all medicines use in these countries (IMS, 2015).

The average annual number of prescription items per person in England increased by 45% from 13 in 2003 to 19 in 2013 (NICE, 2015a). The main reasons for an increase in medicines use and hence polypharmacy, are ageing population and the associated comorbidity as well as rapid advances in medical knowledge and treatment (Hovstadius, Hovstadius, Astrand & Petersson, 2010). The largest consumption is for prescriptions that are used to treat or manage medical conditions of the cardiovascular system (29%), central nervous system (19%), endocrine system (10%) and gastro-intestinal system (9%) (figure 1.2) (NHS Digital, 2018a).

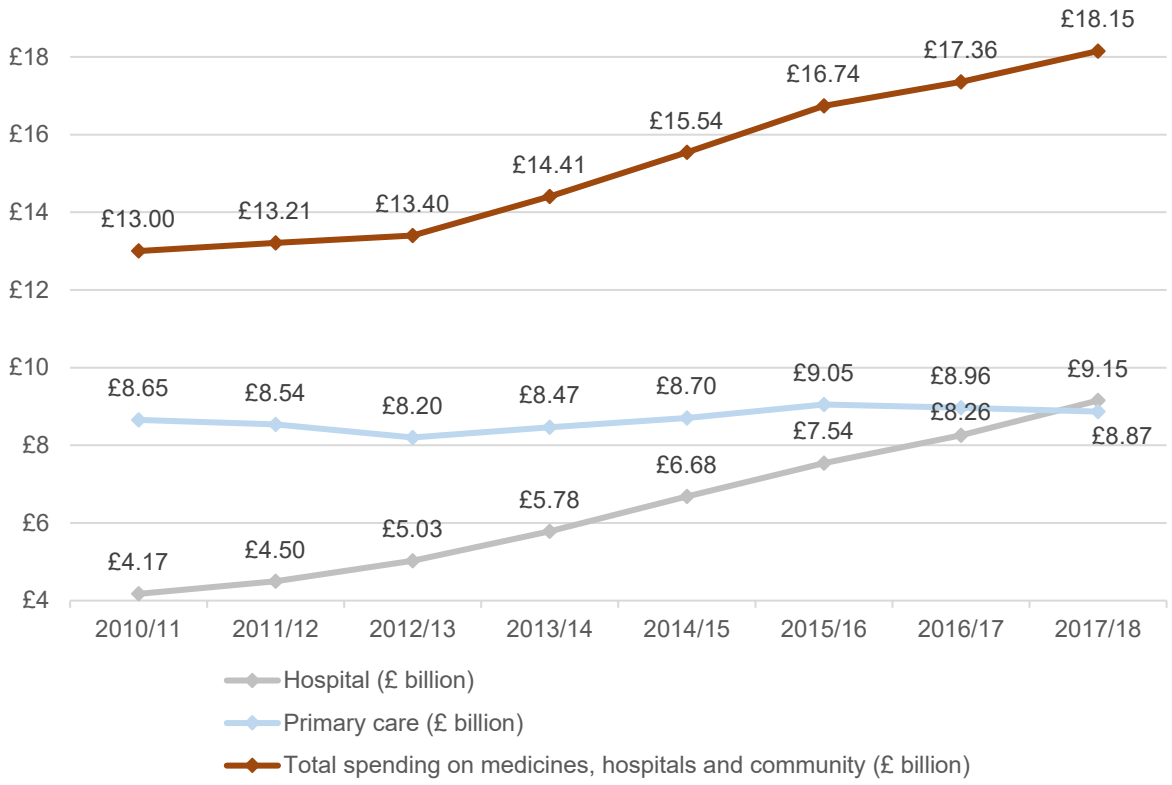
Global spending on medicines is increasing each year, with estimates showing that global spending reached £837 billion[2] in 2017, increased to £884 billion[2] in 2018 and further increased to £957 billion[2] in 2019. Projections from IQVIA estimate that global spending on medicines will be over £1.1 trillion[2] by the year 2023. Although the increase in consumption of medicines is mainly driven by the LMIC, the increase in costs are mainly driven by HIC. These is because the HIC finance more new innovative treatments that are much more expensive compared to generic or non-original branded medicines (IQVIA 2019).

[2] Originally reported in USD at a price base of 2017 and 2018. The cost was converted using the exchange rate from January 2018 (1 USD = 0.7364 GBP) and adjusted for inflation.

Spending on medicines is rapidly increasing in the NHS (figure 1.1). In England the estimated spending on medicines increased from £13 billion in the 2010/11 financial year to £18.15 billion in 2017/18 (NHS Digital, 2018c). The average growth of the spending is 5% each year, which is bigger than the growth in the NHS budget over the same timeframe (Ewbank, Omojomolo, Sullivan & McKenna, 2018). This is mostly driven by increase in costs of prescribing in hospitals. The cost of hospital prescribing in England was £4.2 billion in 2010/11 but increased to £9.15 billion in 2017/18. The average annual growth of the cost of hospital prescribing was around 12% and was so fast that in the financial year 2017/18 hospital prescribing cost the NHS more than primary care prescribing for the first time (NHS Digital, 2018c). This is one of the reasons why the focus of this PhD is on CMR conducted in a hospital setting.

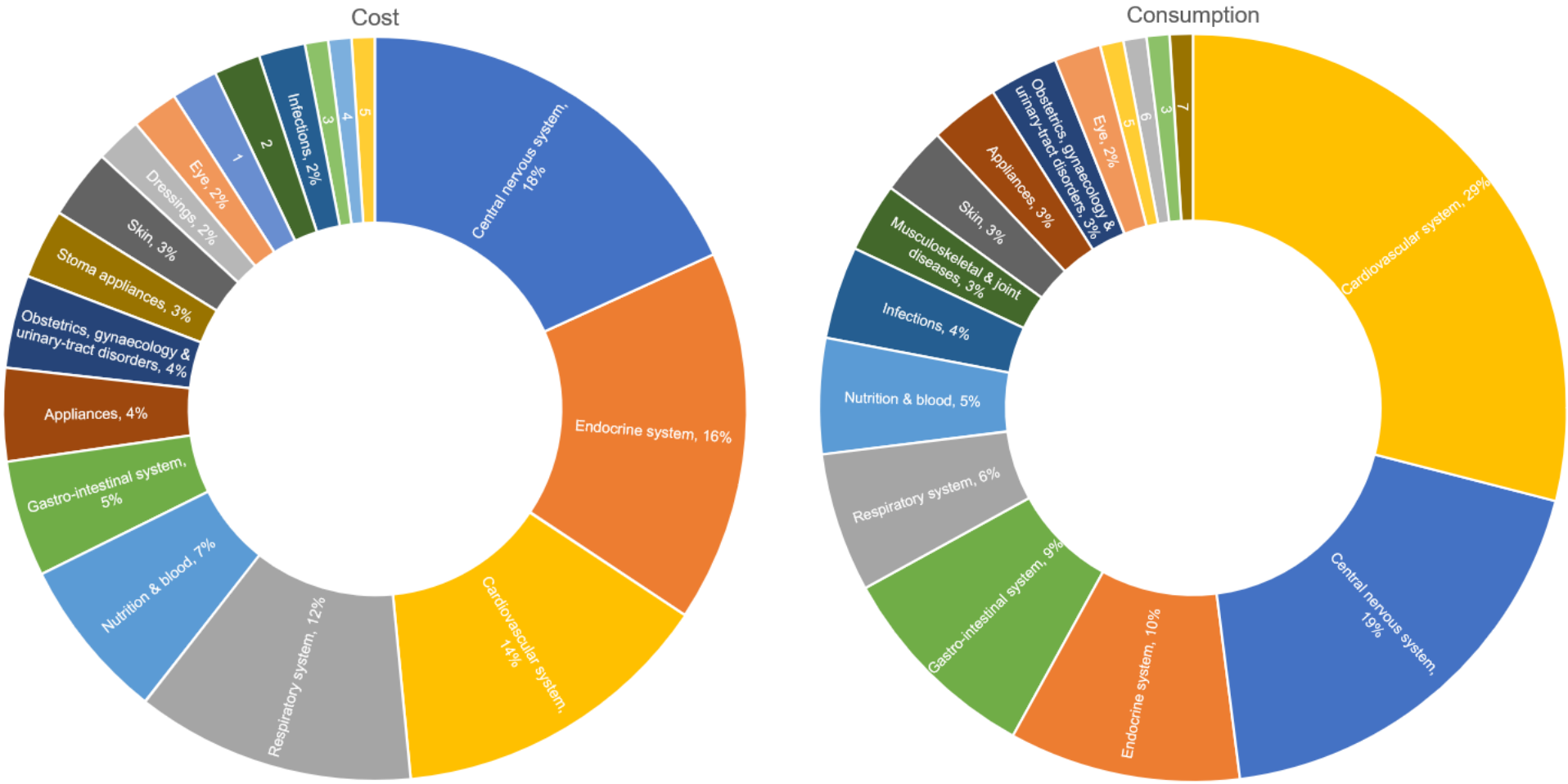
Clinical commissioning groups (CCGs) are NHS organisations that organise and commission health services in England. Data from CCGs show that the biggest costs are incurred for prescriptions that are used to treat or manage medical conditions of the central nervous system (18%), endocrine system (16%), cardiovascular system (14%) and respiratory system (12%) (figure 1.2) (NHS Digital, 2018a).

Figure 1.1 The overall medicines cost in NHS England (hospital and community) from 2010/11 to 2016/17 (£ billions)



Source: (NHS Digital, 2018c)

Figure 1.2 Share of costs and consumption for different prescriptions (classified by BNF chapters), January-March 2018



1. Malignant disease and immunosuppression – cost 2%; 2. Musculoskeletal and joint diseases – cost 2%; 3. Ear, nose and oropharynx – cost 1%, consumption 1%; 4. Incontinence appliances – cost 1%; 5. Immunological products and vaccines – cost 1%, consumption 1%; 6. Dressings – consumption 1%; 7. Stoma appliances – consumption 1%. Source: (NHS Digital, 2018a), PhD author calculations.

1.3.2 Health economics

Health economics is a field of economics with a focus on the 'analysis and understanding of efficiency, effectiveness, values and behaviours involved in the production and consumption of health and healthcare' (York Health Economics Consortium, 2016c). Health economics developed as a separate field of economics based on the distinction between healthcare and other areas of the economy, which includes: barriers to entry, large government intervention, uncertainties in a number of dimensions, third-party agent (physician) and asymmetric information (Arrow, 1963; York Health Economics Consortium, 2016c).

Health economics can be divided into a 'normative branch', which focuses on efficient allocation of scarce resources in healthcare by using philosophy and methodology from economics, and a 'positive branch', which focuses on describing and analysing health-related behaviour without a normative aim (Weisbrod, 1975). Economic evaluations in healthcare are derived from the 'normative' economic theory (welfare economic theory) (Drummond, Sculpher, Claxton, Stoddart & Torrance, 2015).

Welfare economics explores 'methods of obtaining social ordering over alternative possible states of the world' (Boadway & Bruce, 1984; McIntosh, Clarke, Frew & Louviere, 2010). Welfare economics is based on the assumption of individual rationality. It assumes that individuals are the best judges of their own utility and are able to decide whether or not their welfare will be improved by the potential transaction, and based on their preferences they make choices to maximise their own utility (Drummond *et al*., 2015; Perloff, 2018). In welfare economics, the total societal welfare is the sum of individual utility. According to the Pareto criterion, if an individual can benefit without other individuals getting worse, then there is a global improvement in welfare (Boadway & Bruce, 1984; Coast, Smith & Lorgelly, 2008; Culyer, 2014; Drummond *et al*., 2015). However, in healthcare most decisions are between alternatives which provide benefits for some individuals, but additional cost for others (Drummond *et al*., 2015). To address that, health economists apply the Kaldor-Hicks modified Pareto principle, which implies that choosing an option can be seen as a Pareto improvement if the benefit is larger than costs and therefore

individuals who gain from choosing that option could in principle compensate the 'losers' and there will be a net societal welfare gain (Drummond *et al*., 2015).

Healthcare is faced with the challenge of constrained resources available to meet the demand. In a fixed healthcare budget, increase in costs displaces other healthcare services that are already provided. The decisions about what services are provided and for whom have resource implications, where choosing to fund health technology 'A' over health technology 'B' has an opportunity cost attached. The opportunity cost is what is foregone as a consequence of adopting a new health technology. It is measured as the health benefit lost by displacement of services in order to fund the new health technology (Brazier, Ratcliffe, Saloman & Tsuchiya, 2016; York Health Economics Consortium, 2016e).

Economic evaluations are designed as decision support to help decision makers with efficient and equitable allocation of resources by comparing the costs and benefits of health technologies (Brazier *et al*., 2016; Drummond *et al*., 2015). Economic evaluations follow one of two modern approaches: either the 'welfarist' approach or the 'extra-welfarist' ('non-welfarist', or 'decision maker's') approach (Brazier *et al*., 2016).

The 'welfarist' approach aims to maximise societal welfare in relation to societal budget constraints (Buchanan & Wordsworth, 2015). Economic evaluation used in the 'welfarist' approach usually takes the form of cost-benefit analysis (CBA), where health outcomes and costs are expressed in monetary values (more details in section 1.3.2.1 'Economic evaluation in healthcare') (Buchanan & Wordsworth, 2015).

The 'extra-welfarist' approach was driven by a theoretical, ethical and philosophical discussion about value (Sen, 1979). The term 'extra' refers to the added aspect of value that is not covered by the 'welfarist' approach ('population health', 'basic rights', 'the right to a good life', 'quality of life', being able to 'flourish as a person') (Brouwer, Culyer, van Exel & Rutten, 2008; Coast *et al*., 2008). The main economic evaluation used in the 'extra-welfarist' approach is the cost-utility analysis (CUA) where health outcomes are expressed in quality-adjusted life years (QALYs) and the

cost in monetary values (more details in section 1.3.2.1 ‘Economic evaluation in healthcare’) (Brazier *et al*., 2016).

1.3.2.1 Economic evaluation in healthcare

Besides cost-utility analysis (CUA) and cost-benefit analysis (CBA), the other main types of economic evaluations used in healthcare include cost-effectiveness analysis (CEA), cost-minimisation analysis (CMA) and cost-consequences analysis (CCA) (Brazier *et al*., 2016; Drummond *et al*., 2015). These methods compare costs associated with alternative health technologies and the consequences/health outcomes of the alternatives examined in order to estimate their value for money.

The costs included in the analysis can consist of direct costs (for example the cost of medicines or medical equipment or resource use e.g. healthcare professionals’ time) and indirect costs (productivity costs) (Drummond, Sculpher, Claxton, Stoddart & Torrance, 2015; Phillips, 2009). Note that the term ‘indirect costs’ is often used by health economists to describe productivity costs (or lost societal production value), whereas overhead cost (which is termed ‘indirect costs’ in management accounting) is considered part of the direct cost in most health economics literature. The cost of treating patients and its measurement in monetary units is similar for all the analyses, but the choice of how to measure consequences can be considerably different (Drummond *et al*., 2015; Phillips, 2009).

Clinical evaluations use several different measures of health effect for different health technologies. Clinical trials often report intermediate/surrogate outcomes which can help determine whether one health technology is more effective than another, but they are not a measure of health outcome and alone they cannot indicate the magnitude of health improvement. In order to show the health improvement, the intermediate outcomes must be linked to changes in health outcome, for example linking blood pressure in management of obesity to cardiovascular disease mortality (Drummond *et al*., 2015 Jonas *et al*., 2018).

Health can be measured through multiple dimensions; health outcomes such as mortality look at one dimension – ‘the length of life’, whereas quality of life can look at multiple dimensions of health. Different measures of health-related quality of life

(HRQoL) cover different aspects and different dimensions of health; these can be generic or disease specific descriptions of HRQoL (Drummond *et al*., 2015).

The classification of measures of health effects is presented below:

1. Intermediate outcomes:
   For example: reduction in blood pressure, cases detected, cluster of differentiation 4 (CD4) count.
2. Final outcomes:
   a. Single dimension – for example: mortality rate, survival rate, event rates (e.g. stroke).
   b. Multiple dimensions:
      - Generic (for example questionnaires such as the European Quality of Life (EuroQoL) Five Dimensions questionnaire (EQ-5D), where the dimensions are: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, or the Short-Form (36) Health Survey (SF-36)).
      - Disease specific (for example Expanded Disability Status Scale (EDSS) or European Organization of Randomized Controlled Trials 8 Dimension (EORTC-8D) questionnaires)

(Drummond *et al*., 2015)

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is a method mostly used when a decision maker with a given budget is considering a limited range of potential health technologies in a given field (Drummond *et al*., 2015). In CEA, the consequences of different health technologies are measured using a single outcome measured in ‘natural’ units. The outcome measure can be intermediate outcomes and single dimension final outcomes. The results may be presented as the incremental cost-effectiveness ratio (ICER), where the difference in cost between health technologies is divided by the difference in the effects. ICER is expressed as incremental cost per unit of effect (for example extra cost per one case of disease detected). The results can also be expressed as effects per unit of cost (for example life-years gained for each pound spent) (Drummond *et al*., 2015).

The advantage of CEA is that the outcome used in the analysis can be more disease specific and can be easily explained to the decision makers. However, the biggest disadvantage of CEA is that, because the measures of effect can be specific to a health technology or disease, it is difficult to assess the opportunity cost of other programmes covered by the same budget which use different effect measures (Drummond *et al*., 2015).

Cost-utility analysis

Cost-utility analysis (CUA) is similar to CEA; one can even argue that it is a type of CEA. CUA follows the same principles as CEA and the difference is in the type of outcome used in the analysis (Drummond *et al*., 2015). The unit of health effect in CUA is 'a year in full health', which is most commonly measured as quality-adjusted life years (QALYs). QALY is calculated by multiplying an individual's life expectancy by the value of the HRQoL, which is usually measured on a scale between 0 (dead) to 1 (full health) (Brazier *et al*., 2016). HRQoL can also be negative when health state worse than death is experienced (Sullivan, Hansen, Ombler, Derrett & Devlin, 2020). When patients transition between states of health, then QALYs are the product of time spent in each of the health states and the utility score of HRQoL for given states (Brazier *et al*., 2016; Graves *et al*., 2016).

The advantage of CUA over CEA is that QALYs can at the same time capture the gains from reduced mortality and morbidity (looking at multiple dimensions of health) and combine them into a single measure (Drummond *et al*., 2015). This allows the decision maker to compare health technologies affecting more than one dimension of health, health technologies for the same health conditions that impact on different dimensions of health, and health technologies for different health conditions with each other, as they have a common denominator (Brazier *et al*., 2016).

The process for estimating QALY consists of two parts: the first is describing the state or time profile of a person's movement between health states; the second is the valuation of that patient's trajectory (Brazier *et al*., 2016). Economic evaluations incorporate generic preference-based measures of health such as the European Quality of Life (EuroQoL) Five Dimensions (EQ-5D) questionnaire, the Health Utilities Index Mark 3 (HUI3) questionnaire or the Short-Form Six-Dimension (SF-6D)

questionnaire. The questionnaires are completed by patients or carers, but the weights are typically defined by a representative sample of the national population, so that the prioritisation is in accordance with the preferences of the general population, but not necessarily with the group of patients' own preferences. In fact, research has shown that patients often value health states they reside in differently from and higher than the average population (Brazier *et al*., 2016; Drummond *et al*., 2015).

As with CEA, the results of CUA can be expressed as a cost per unit of benefit (cost per QALY) and can be summarised using the incremental cost-effectiveness ratio (ICER). The ICER is calculated by dividing the difference in cost between the new health technology and the comparator by the difference in QALYs between the new health technology and the comparator (Drummond *et al*., 2015). Health technologies which cost less and provide greater QALY gain are considered dominant over comparators and are cost-effective. If the health technology costs more and provides less benefit, it is dominated by the comparator and is not cost-effective. Health technologies which cost more but at the same time provide more benefit are the most common scenario and their cost-effectiveness may be interpreted based on the cost-effectiveness threshold. If ICER is below the threshold, the health technologies are usually deemed cost-effective (Drummond *et al*., 2015; Klok & Postma, 2004).

In theory, the threshold should represent the opportunity cost to society of accepting a new health technology, that is the cost of a QALY elsewhere in the healthcare system. In practice, cost-effectiveness thresholds can be set by health technology assessment agencies of a given country (either implicit or explicit) and the World Health Organization has suggested ways to define national thresholds. I describe the threshold used in the UK in section 1.3.2.3 of this chapter.

Finally, new health technologies can sometimes cost less, but at the same time provide less benefit than existing technologies. Not all countries consider these health technologies based on an ethical stand that even though new health technologies are less expensive they do not provide equal or greater benefit compared to the current standard of care.

Cost-benefit analysis

Cost-benefit analysis (CBA) is also similar to CEA, where the difference lies in the way in which health consequences of the intervention are expressed. In CBA, both the cost and the outcomes are expressed in monetary values (Brazier *et al*., 2016; Drummond *et al*., 2015). The biggest advantage of this approach is that the decision maker can directly compare the incremental costs with the incremental health consequences of the given health technology. The decision criterion is also much simpler: if a new technology provides higher benefits than costs, the decision should be to implement the new technology.

CEA and CUA are methods used to maximise value for money within an existing budget, however they do not consider whether it is worthwhile expanding the budget. CBA is a method that can facilitate that, by broadening the concept of value and expressing the health consequences in monetary values (Drummond *et al*., 2015). CBA is based on the principles of welfare economics, where the source of value is the individual consumers (Brazier *et al*., 2016; Drummond *et al*., 2015). The biggest disadvantage of CBA is the difficulty in associating monetary value with health outcomes. Valuation of health outcomes can be done through techniques such as willingness to pay surveys, human capital approach, value of a statistical life and discrete choice experiments (Brazier *et al*., 2016; York Health Economics Consortium, 2016a).

Cost-minimisation analysis

Cost-minimisation analysis (CMA) is implemented under the assumption that health technologies which are compared provide the same benefit and are associated with the same risks (Brazier *et al*., 2016). Because of uncertainty associated with the effectiveness of health technologies, CMA is not usually recommended, as assumption that health technologies have equal effect can be too uncertain. Therefore, conducting a CMA should be limited to situations in which prior research has determined that the health technologies provide equal effect. The assumption can be true for very similar health technologies, for example medicines from the same pharmacological class (Drummond *et al*., 2015).

CMA can determine which treatment provides the same outcome for lower costs and thus in CMA the least expensive option is preferred (Haycox, 2009; York Health Economics Consortium, 2016b). The equivalent benefit of both intervention and comparator should be sustained over time and not vary with different observation times (Haycox, 2009). For CMA to be conducted, all the outcomes should be equal or similar for both intervention and comparator. The primary outcome must provide the main benefit of the intervention and the comparator and any differences in secondary outcomes should not be clinically significant because even if the intervention and comparator are equal in terms of efficacy and safety, one of the health technologies may provide other benefits such us a more convenient method of administration (Hatala, Holbrook & Goldsmith, 1999; Haycox, 2009).

Therefore, the analysis is limited to the cost associated with the health intervention and the comparator. To determine the costs of all the health technologies being compared, the same methods are used as in cost-effectiveness analysis (Haycox, 2009).

Cost-consequence analysis

Cost-consequence analysis (CCA) is one of the simplest forms of health economic evaluation. It was created by Mauskopf, Paul, Grant & Stergachis (1998) in order to provide a new way of presenting results of economic evaluations to decision makers.

CCA lists all the relevant costs and health- and non-health-related effects and presents them without aggregation. It can be used as a first step that informs the cost-effectiveness analysis about all the costs and consequences of adapting a new intervention or it can be used when different outcomes cannot be merged into a health utility index measure. The advantage of CCA is that all the benefits can be considered including benefits not related to health outcomes, or benefits that cannot be expressed in monetary values. Another advantage of CCA lies in its simplicity, because it provides a transparent way to present results to the decision makers (Craig, Shore, Russell & Jenks, 2019).

However, CCA is not based on welfare economic principles, because it does not provide information for decision makers on how to maximise value for money. It is not possible to maximise utility for individuals, as the list of outcomes/consequences

is not based on any measure of preference. The outcomes are not aggregated in one single measure such as quality-adjusted life years or in monetary values; the outcomes are shown as a list of natural units and based on this the decision maker can subjectively decide whether the interventions' benefits are worth the cost (Optimity Advisors, 2016).

Summary of economic evaluations in healthcare

Different health economic evaluations can be used to provide decision makers with information that may help determine the value for money of the health technology being assessed in relation to the comparator. Table 1.1 summarises the key differences between all five methods described in this section.

In the PhD, I use two types of analysis: (1) cost-effectiveness analysis in chapter 4, where the ICER is measured as cost per emergency department (ED) reattendance avoided and (2) cost-utility analysis in chapter 6, where ICER is expressed as cost per QALY gained.

Table 1.1 Comparison of methods for economic evaluation in healthcare

Type of analysis	Cost	Outcomes
Cost-effectiveness analysis (CEA)	Monetary values	Single natural unit (e.g. blood pressure, life years gained etc.)
Cost-utility analysis (CUA)		Healthy years (QALYs)
Cost-benefit analysis (CBA)		Monetary values
Cost-minimisation analysis (CMA)		Assumption of equal benefit of new intervention and comparator
Cost-consequence analysis (CCA)		List of different health and non-health related outcomes of an intervention

QALY, quality adjusted life year.

1.3.2.2 Decision models used for health economics

Health economic models use mathematical relationships to estimate the costs and health gains of alternative interventions. Several models can be used to evaluate the cost-effectiveness and cost-utility of a given health technology. Depending on

whether the model describes the experience of an 'average' patient or whether it considers the individual characteristics of each patient, models can be classified as:

1. Cohort models:
    - Decision tree model;
    - Markov cohort model;
    - System dynamics model.

2. Individual models:
    - Microsimulation;
    - Agent based model;
    - Discrete event simulation.

(Hoang *et al*., 2016)

In the cohort models, individual patients are aggregated into one cohort which consists of patients with similar characteristics (e.g. age and disease type). As the model runs, a proportion of patients move between different states in the model, creating subgroups of patients, for example based on the severity of their disease or mortality. In the individual models, the model runs for individual patients with their own set of characteristics. The outcomes are then combined into an average across a large sample of patients (Briggs, Sculpher & Claxton, 2006; Drummond *et al*., 2015; Hoang *et al*., 2016).

Economic models need to be sufficiently sophisticated to accurately capture the main aspects of a decision problem, disease process and intervention (Weinstein *et al*., 2003), but simple enough to provide results in a timely manner using currently available evidence (K. Claxton, Ginnelly, Sculpher, Philips & Palmer, 2004). This can be achieved by minimising the number of states in the model to the most essential (Brennana, Chick & Davies, 2006).

For the cost-effectiveness and cost-utility analyses of CMR (from chapter 4 and 6 of the PhD thesis), I used the two most common types of modelling methods – the decision tree model and the Markov model.

The decision tree model is a decision model which has a structure that represents clinical pathways. At the root of the decision tree there is a decision node represented by a square symbol. The branches of the decision node indicate decision between alternative treatment options being compared. For each branch there is a series of chance nodes, each represented by a circle symbol, which indicate the pathway for mutually exclusive sequences of events. There is probability of patients passing along each of the pathways, which is calculated by multiplying the probability of the initial branch by subsequent conditional probabilities. Each of the pathways also have cost attached to them, which represents the sum of costs patient experience in the pathway. These events lead to an outcome, which can have a cost and health gain/loss attached to it (Drummond *et al*., 2015).

The Markov model is a time dimension, stochastic model centred around Markov states. As with the decision tree model, the Markov model also represents clinical pathways, however it is done through a finite set of Markov states. For example, a simple Markov model can consist of three states: asymptomatic, progression of disease, death. Each state has a utility value and cost value attached to it. The patient moves between these states based on the probability of an event occurring during a defined period called the cycle.

The Markov states in the model are chosen for specific disease processes based on their clinical and/or economic importance. The Markov states are mutually exclusive, meaning that modelled patients can only be in one state at any given time (Drummond *et al*., 2015). The Markov states should “reflect the biological/theoretical understanding of the disease or condition modelled” (Siebert *et al*., 2012) and account for difference in cost and/or prognosis and/or utility.

The time in the model progresses in discrete stages (cycles), which means the changes are only identified during these intervals. The cycle length determines the point at which observation of the proportion of patients in different health states occurs (Chhatwal, Jayasuriya & Elbasha, 2016; Drummond *et al*., 2015). The length of the cycle should be clinically meaningful and short enough to capture all the clinical events and interventions (Siebert *et al*., 2012).

1.3.2.3 NICE guidelines for economic evaluation in the United Kingdom

The National Institute for Health and Care Excellence (NICE) is the executive non-departmental public body in the UK, sponsored by the Department of Health and Social Care. NICE serves the English and Welsh NHS and is the main institution that makes decisions as to whether an intervention should be deemed cost-effective (Drummond *et al*., 2015; NICE, 2013b). NICE technology appraisal guidance is used to make recommendations about medicines, medical devices, health promotion activities, surgical procedures and diagnostic techniques (NICE, 2013b). Health technology appraisal serves the purpose of assuring that only interventions that improve the health status of a population are funded by the NHS. An extra-welfarism perspective has influenced health economics research in the UK, where it is mandatory for local decision makers to consider economic evaluations conducted by the NICE when making commissioning decisions (Coast *et al*., 2008).

The recommended approach in conducting an economic evaluation of health technologies is described in the Guide to the methods of technology appraisal (NICE, 2013b). The guide presents the 'reference case', which is a formal statement of methods and assumptions that are accepted by NICE. The NICE 'reference case' assures consistency between economic evaluations of health technologies. Evaluations which do not follow the 'reference case' are permitted by NICE, however a justification is required as to why this deviation occurred (York Health Economics Consortium, 2016e). Some things are not recommended by NICE either in the 'reference case' or 'non reference case' analyses, such as inclusion of productivity costs (NICE, 2013b).

In the 'reference case', NICE details that the first step when considering the economic impact of new health technology is to describe the decision problem, which indicates the target population, the health technologies being compared and the expected place of the new technology in the current treatment pathway. When choosing a comparator, NICE looks at the established health technology in NHS practice in England, existing NICE guidance, the cost-effectiveness of the comparator, the natural history of the condition without suitable treatment and the licensing of the comparator. The perspective used in the NICE 'reference case' for outcomes is that of patients and/or carers, whereas for cost, the perspective should

be that of the NHS and personal and social services (PSS). The recommended economic evaluation is the cost-utility analysis with a time horizon long enough to reflect all important differences in costs and/or outcomes. The synthesis of evidence should be based on systematic literature review. The QALYs are the preferred option as a health outcome in the NICE 'reference case'. To calculate QALYs, NICE recommends using HRQoL reported by patients and/or carers using the EQ-5D questionnaire. The changes in HRQoL should be valued by a representative sample of the UK population. The evidence about costs should relate to both NHS and PSS resource use and should be valued using relevant prices. For both health outcomes and costs NICE recommends using an annual discounting rate of 3.5% (NICE, 2013b).

In order to estimate which health technologies are cost-effective, countries introduce cost-effectiveness thresholds and if the ICER is below that threshold the interventions are usually deemed cost-effective. NICE uses a cost-effectiveness threshold that is between £20,000 and £30,000 per one QALY gained (McCabe, Claxton & Culyer, 2008). In most cases, health technologies that cost below £20,000 per QALY are recommended for funding. For health technologies where ICER is between £20,000 and £30,000 per QALY, the decision regarding funding depends on other factors such as uncertainties and innovation of the health technology. Health technologies which cost above £30,000 per QALY are usually not recommended for funding, but could be if other factors considered by NICE are stronger (Brazier *et al*., 2016).

For years now there have been numerous discussions about what the threshold value should be. The NICE thresholds have been criticised for being too high and for not providing enough value in assessing the trade-offs that face decision makers about reimbursing health interventions. Research led by Prof. Karl Claxton suggests that interventions with ICER over £13,000 per QALY can lead to more harm than improvement for the NHS, as financing them displaces money from more effective healthcare interventions (opportunity cost to society) (Karl Claxton *et al*., 2013; Dillon, 2015; Marseille, Larson, Kazi, Kahn & Rosen, 2015). NICE recently introduced a fast track appraisal, for which health technologies with a likely ICER

below £10,000 per QALY are deemed to be offering exceptional value for money (NICE, 2017; Timmins, 2017).

1.3.2.4 Economic evaluation of complex interventions

The methods of economic evaluation described in section 1.3.2.1 have primarily been applied to pharmaceuticals as the formal requirement for assessment of cost-effectiveness of new medicines on the market (Drummond *et al*., 2015). However, these methods have been used for other health technologies, including procedures, medical devices, digital health technologies, public health interventions and new models of care (Drummond *et al*., 2015; Husereau *et al*., 2014). Seeing the value of economic evaluation, decision makers and researchers started using them to make decisions about adoption of complex interventions in healthcare. However, researchers encountered a number of challenges when applying the standard economic evaluations to complex interventions.

Challenges of conducting economic evaluations of complex interventions

The results of the cost-effectiveness analysis of complex interventions may have limited generalisability, as complex interventions tend to be context dependant and tailored to the local setting in which they are delivered. Complex interventions have multiple interacting components and not all the components are replicated when the intervention is scaled up. Because complex interventions can be tailored to specific settings, they can be successful in one setting and unsuccessful in another, which makes it difficult to establish whether they provide value for money based on a single study (Craig, Dieppe, Macintyre, Michie, *et al*., 2008; Dixon-Woods, Leslie, Tarrant & Bion, 2013; Oliveira, 2014; Sculpher *et al*., 2004). Therefore, the wrong conclusion about cost-effectiveness can be drawn from a local trial/model because of lack of transferability.

The challenge is also how we measure the final health outcome of complex interventions (see classification of outcomes in section 1.3.2.1 ‘Economic evaluation in healthcare’). Usually in economic evaluations researchers use QALYs as the measure of health benefit. QALYs are the gold standard as they allow for comparison between a whole spectrum of health technologies and interventions. However, with complex interventions, QALYs may be insufficient to capture all the

benefits that the intervention provides. For example, the effects of public health interventions may go beyond a single individual, with a wider population level effect, whereas QALY is a measure of effect for a single individual. But even at a single individual level interventions can provide benefits which cannot be captured in QALY gain, such as: improving patient experience, process efficiency, health literacy, change in behaviour or access to services (Oliveira, 2014; Payne, McAllister & Davies, 2013). That is why when estimating the cost-effectiveness impact of complex interventions we can sometimes miss significant effects of interventions. Even with complex interventions that can have their benefit expressed in QALYs it can be challenging to measure that benefit. Complex interventions often have multiple mechanisms that lead towards achieving the QALY gain and therefore it may be useful to measure intermediate outcomes to understand how these mechanisms work. However, because the mechanisms of complex interventions are not linear in many cases it is difficult to link intermediate outcomes to final outcomes (e.g. QALYs) and some estimations made can be highly uncertain (Husereau *et al*., 2014; Oliveira, 2014).

Another challenge of health economic evaluation of complex interventions is that often there is limited evidence about complex interventions. The lack of evidence can be due to the complexity of the intervention itself where it is hard to prove causality for interventions with multiple interacting components (Craig *et al*., 2018). Other complex interventions such as precision medicines, which work only for certain groups of patients based on their genetic, environmental, and lifestyle factors, can be difficult to evaluate using traditional research methods (Love-Koh *et al*., 2018). Moreover, the difficulty in gathering evidence about complex interventions is also due to the fact that complex interventions are often under researched. Before receiving market access medicines require large multicentre trials to prove their effectiveness and safety; this is not the case with complex interventions, which often have to rely on single trials and non-randomised studies (Husereau *et al*., 2014). This is because the majority of studies of medicines are financed by the pharmaceutical industry, whereas complex interventions have to attract funding from the public health sector.

Randomised control trials (RCTs) are the gold standard for economic evaluations. They are based on the principle that all contextual factors are removed/controlled for and patients are randomised to treatment or control groups, which implies that the groups are equal and the only difference is in the patient receiving or not receiving the treatment (Blackwood, 2006; Oliveira, 2014). A common challenge with complex interventions is omitting discussion on implementation barriers or unintended consequences of interventions (Brainard & Hunter, 2016). In principle, the mechanism of interventions might provide benefit for patients, but because it is delivered in a complex system the implementation barriers might prevent the benefits being seen in studies. It can also be the other way around, where controlled studies can show that an intervention provides benefits for patients, but when the intervention is scaled up, the benefit cannot be translated to a different setting (Craig *et al*., 2018; Dixon-Woods *et al*., 2013). The success of complex interventions is dependent on contextual factors, hence RCTs may not always capture the benefits of complex interventions within each setting. This is true for interventions which can be tailored and flexible, where behaviours are important and where learning is present (Oliveira, 2014). Using multiple methodologies to evaluate complex interventions can lead to a comprehensive and more robust understanding of their economic value (Oliveira, 2014).

Approaches to economic evaluation of complex interventions

Complexity of an intervention or the system in which it is delivered should not prevent researchers from making good quality economic evaluations, however it can add significant difficulty in doing such research (Husereau *et al*., 2014). It is important to maintain scientific validity of economic evaluations at the same time as recognising that complexity of these interventions can require deviations from and modification of traditional economic evaluations (Byford & Sefton, 2003).

Health economists have described the issue of complexity in economic evaluations in a number of ways. Some researchers acknowledge the challenges of using current methods of economic evaluation in relation to complex intervention, but argue that these methods can still be used if the researcher is aware of the limitations of their study. Other health economists have conducted methodological research to address some of the challenges of conducting economic evaluation of

complex intervention. These include, for example, new types of instruments for measuring health outcomes or new approaches to measuring QALYs. Literature also describes theoretical research on special issues/aspects of complexity such as the 'generalisability' of the economic impact of a complex intervention from one study to the whole population (Craig *et al*., 2006, 2018; Craig, Dieppe, Macintyre, Michie, *et al*., 2008; Dixon-Woods *et al*., 2013; Love-Koh *et al*., 2018; Oliveira, 2014; Sculpher *et al*., 2004; Udsen, Lilholt, Hejlesen & Ehlers, 2017).

Many health technology assessment (HTA) agencies acknowledge the issue of complexity in economic evaluations. The NICE 'reference case' (NICE, 2013b) presents the gold standard in conducting cost-effectiveness analysis of health technologies in the UK. However, the process is sometimes not suitable for evaluation of more complex interventions. NICE allows deviation from their 'reference case' when the reasons for not applying these methods are clearly specified and justified and the implications are quantified (NICE, 2013b). NICE also publishes recommended research methods for different types of health technologies, which can be complex interventions such as the recently published Evidence standards framework for digital health technologies (NICE, 2019). The solutions proposed by NICE allow minor adjustments in existing health economic methods, but do not offer specific guidelines on how to approach economic evaluation of complex interventions.

The Canadian HTA Agency, the Institute of Health Economics (IHE), has published a discussion paper on economic evaluation of complex health systems interventions (Husereau *et al*., 2014). IHE, similarly to NICE, requires all analyses to follow its 'reference case' and the researchers are at liberty to conduct additional analyses using other methods for the specific decision problem. In the paper, IHE recognises some of the key challenges in conducting economic evaluation of complex interventions but suggests that standard economic evaluation of health technologies can be applied to any complex intervention if special considerations are undertaken. These considerations have been summarised in six key areas:

1. Type of evaluation and valuing outcomes – complex intervention may have multiple outcomes that are relevant for the decision problem that are not always possible to express in QALYs.

2. Comparators – special consideration should be given to the comparator of complex intervention (lack of intervention, different components of the intervention, sequence in which components are introduced etc). Researchers are encouraged to compare complex interventions with usual care and as additional analyses other comparators can be used.
3. Perspective – complex interventions may impact on different stakeholders and costs outside the healthcare system. Different perspectives may be considered by researchers.
4. Effectiveness – outcomes of complex interventions may be context dependant and researchers should acknowledge the limitations of evidence about the effectiveness of complex interventions and its generalisability to different settings.
5. Resource use and costs – when valuing resource use and costs, researchers should consider that they might be variable, context dependant and associated with an individual component of the intervention.
6. Modelling – for understanding the impact of various components of complex interventions, economic models can consist of a wide range of different care pathways.

The economic evaluations conducted as part of this PhD follow the principles of welfare economics and NICE Guide to the methods of technology appraisal (NICE, 2013b). To address the challenges with economic evaluations of complex interventions, special considerations regarding the six issues described by IHE (Husereau *et al*., 2014) were taken.

1.3.3 Literature about cost-effectiveness of medication review

The cost-effectiveness of medication review in UK NHS hospitals is so far unknown. In 2015, NICE undertook a systematic literature review of health economic studies regarding medication reviews (NICE, 2015a). After screening 1,507 studies, six studies about pharmacist-led medication reviews were included. The review did not identify studies looking at medication reviews conducted by other healthcare professionals. Additionally, I have identified three further health economic studies of medication reviews published after the NICE guideline. The studies included

medication reviews conducted by pharmacists, but also by pharmacy interns, pharmacy technicians and multidisciplinary teams.

Of the nine studies (table 1.2), six were based in a community setting (GP surgery, community pharmacy, patient's home or a phone call with the patients) and three studies looked at the hospital setting. However, none of the studies looked at the hospital setting from the UK NHS perspective. All but two studies were analysis conducted alongside an RCT or prospective controlled study. The remaining two were: (1) a study based on unpublished quality improvement data and (2) analysis based on a before and after study.

Community setting

Of the studies that looked at the cost-effectiveness of CMR delivered in a community setting, two studies with minor limitations (Chinthammit *et al*., 2015; Pacini, Smith, Wilson & Holland, 2007) reported that CMR compared to no intervention was not cost-effective. Of the remaining four studies with serious limitations, three (Bond *et al*., 2007; Sellors *et al*., 2003; The Community Pharmacy Medicines Management Project Evaluation Team, 2007) reported that CMR was cost-incurring and one (Desborough, Sach, Bhattacharya, Holland & Wright, 2012) reported that it was cost-saving.

Hospital setting

There were three cost-effectiveness analyses alongside clinical trials of medication review done in a hospital setting outside the UK. Two studies concluded that CMR was a cost-effective intervention and one concluded that CMR was not cost-effective.

1. (Gallagher *et al*., 2016) – the most recent study from Ireland was conducted alongside a cluster RCT for patients ≥ 65 years old admitted to an emergency department. The results indicated that CMR dominated over usual pharmaceutical care by proving more benefits at lower cost. The probability of CMR being cost-effective was 78% at a threshold of €5,000 per QALY.
2. (Ghatnekar, Bondesson, Persson & Eriksson, 2013) – the study was conducted alongside a prospective controlled study in Swedish internal medicine wards on

patients ≥ 65 years old. The study used a decision tree model to conclude that the probability of CMR being cost-effective at a €0 per QALY threshold compared to usual care was 98%.

3. (Wallerstedt, Bladh & Ramsberg, 2012) – the only study which concluded that CMR was not cost-effective. The study was conducted alongside an RCT in Swedish internal medicines wards on patients > 72 years old, on ≥ four medicines. The CMR provided more benefit, but at greater cost, and the probability of CMR being cost-effective was 20% at the threshold of €50,000 per QALY.

Table 1.2 Medication review – economic evidence

Study	Population	Medication review		Comparator	Time horizon	Perspective	Type of analysis	Results
		Healthcare professional	Setting					
(Gallagher *et al*., 2016)	Patients ≥ 65 years, admitted to emergency department	Pharmacist	Hospital acute care	Usual care	Until patient's discharge or 10-day follow-up, whichever came first	Irish healthcare provider (Health Service Executive)	Cost-effectiveness analysis alongside a cluster RCT	Medication review was cost-saving and provided greater QALY gain. The probability of medication review being cost-effective was: 71% at €0 and €250 thresholds 72% at €500, €750 and €1,000 thresholds 79% at €5,000 threshold

(Chinthammit *et al*., 2015)	Medicare Part D patients with ≥ 3 chronic conditions & ≥ 3 medications & annual medication cost > $3,100 & ≥ 1 medication-related problem	Pharmacist, pharmacy interns and pharmacy technicians	Phone call by medication management center staff	Non-comprehensive medication review	12 months	USA healthcare payer	Cost-effectiveness analysis based on unpublished quality improvement data and additional modelling based on systematic literature review	Medication review was dominated by the comparator.
(Ghatnekar *et al*., 2013)	Patients ≥ 65 years, admitted to internal medicine wards	Multidisciplinary team including a pharmacist	Hospital – internal medicine wards	Usual care	3 months	Not reported	Cost-utility analysis alongside prospective controlled trial	The medication reconciliation and medication review were cost-saving and were associated with greater QALY gain compared to usual care.

(Desborough *et al*., 2012)	Patients > 65 years	Pharmacist	Patient's home	No intervention	6 months	UK NHS	Cost consequence calculations based on before and after study	Medication review was cost-saving, reduced emergency hospital admissions and increased medication adherence. There was no significant effect of medication review on quality of life.
(Wallerstedt *et al*., 2012)	Hospitalised patients > 72 years, on ≥ 4 medicines	Pharmacist	Hospital – internal medicine wards	Usual care	6 months	Swedish healthcare system	Cost-utility analysis based on RCT	The probability of medication review being cost-effective was 20% at £50,000/QALY threshold
(Bond *et al*., 2007)	Patients < 65 years, on medication for hypertension or angina	Pharmacist	GP surgery	Usual care	12 months	UK NHS	Cost consequence calculations based on RCT	Medication review was cost incurring

(Pacini *et al*., 2007)	Patients > 80 years, on ≥ 2 medications, with a recent hospitalisation	Pharmacist	Patient's home	Usual care	6 months	UK NHS	Cost-utility analysis based on RCT	The probability of medication review being cost-effective was 25% at £30,000/QALY threshold
(The Community Pharmacy Medicines Management Project Evaluation Team, 2007)	Patients > 17 years, with coronary heart disease	Pharmacist	Community pharmacy	Usual care	12 months	UK NHS	Cost-utility analysis based on RCT	Medication review was cost incurring with no statistically significant increase in HRQoL
(Sellors *et al*., 2003)	Patients ≥ 65 years, on ≥ 5 medications. Seen by the GP within 12 months. With no evidence of cognitive impairment.	Pharmacist	Family practice	Usual care	5 months	Ontario, Canada healthcare system	Cost consequence calculations based on RCT	Medication review was cost incurring

NHS, National Health Service; RCT, randomised controlled trial; QALY, quality-adjusted life year; GP, general practitioner.

1.4 Gaps in the literature and rationale for the PhD

1.4.1 Economic evidence is unavailable for medication review done in UK hospitals

The PhD project will contribute to scientific knowledge by providing previously unavailable information about the cost-effectiveness of CMR in the UK NHS hospital setting. Evidence about the cost-effectiveness of CMR would be an important contribution to scientific knowledge, as even though NICE recommends conducting CMR, the uptake of the intervention is currently low. Figures suggest that as few as 4% of eligible patients receive CMR in hospitals (Szymanski *et al*., 2016; Ward *et al*., 2019). Therefore, an understanding of whether CMR is a cost-effective intervention can support decisions about investment of resource to increase CMR implementation.

Most of the economic evidence about CMR comes from studies of CMR delivered in the community setting (six studies). The cost of the intervention might differ significantly between a CMR carried out in hospital and one carried out in the community (e.g. travel cost of the healthcare professional, difference in cost of hospital pharmacist vs community pharmacist vs general practitioner lead intervention etc.) Moreover, the target population of patients who receive the intervention differs between CMR in hospital and in community settings. Patients in hospitals may be older people who are acutely admitted to hospital with a high readmission risk. The population of patients receiving CMR in their own home, GP surgery or community pharmacy may be in overall better health than those receiving CMR in hospitals.

The three studies about cost-effectiveness of CMR in a hospital setting come from Ireland and Sweden (Gallagher *et al*., 2016; Ghatnekar *et al*., 2013; Wallerstedt *et al*., 2012); there are currently no UK-based studies.

Moreover, the current available studies have methodological limitations. There were no studies based primarily on systematic literature review and modelling of cost-effectiveness; this can have severe limitations for the generalisability of these

studies (Sculpher, 2015). Most of the studies were studies alongside RCT. This approach means that the results of the study only relate to the population included in the study and the time horizon of the analysis is defined by the trial's follow-up period. Moreover, analysis based on a single RCT does not incorporate all the available evidence. This is clearly seen in all nine studies, where there is wide variation between the populations of each study and there is no analysis beyond a 12-month time horizon. Furthermore, not all the relevant evidence is taken into account, which is why the results from the nine studies are not consistent with each other (Sculpher, 2015).

NICE stated that economic evidence on the cost-effectiveness of medication reviews carried out by healthcare professionals other than pharmacists is not available. NICE recommended conducting research on the economic impact of medication reviews delivered by other healthcare professionals or multidisciplinary teams.

To summarise, the PhD project will contribute to scientific knowledge in three ways:

1. **The PhD will be the first study of cost-effectiveness of CMR in the context of UK NHS hospitals.**

   In the guideline on Medicines optimisation (NICE, 2015a), NICE based its recommendation on cost-effectiveness studies done in community settings or studies done in hospitals outside of the UK. However, the cost of providing healthcare in a community setting differs from the cost in hospitals. The same is true for countries, where the cost of providing healthcare differs from country to country, so something that can be cost-effective in one country may not be cost-effective in another (Anderson, 2010; Donaldson, Mugford & Vale, 2002). My PhD project will use UK NHS costs and data from UK registries to determine the cost-effectiveness of CMR for the hospital setting in the UK.

2. **The cost-effectiveness analysis of CMR in the PhD will address common methodological limitations of current evidence.**

The PhD will be the first study which is based primarily on systematic literature review and which uses evidence synthesis, decision analytic modelling and lifetime time horizon for modelling.

The studies of cost-effectiveness of CMR in hospitals which were carried out in other countries were trial-based CEA, for which limitations are:

- External validity of RCTs – results relate only to the population included in the trial;
- Only the clinical and resource evidence from those RCTs are included;
- The time horizon is defined by the RCT's follow-up period.

These characteristics are not consistent with the key criteria for evidence-based decision making when evaluating the cost-effectiveness of CMR (Sculpher, 2015).

The PhD project will overcome these methodological limitations:

- External validity – this was addressed by using modelling. The relative treatment effect comes from trials (hazard and relative risk ratios), but is then applied to a baseline measure, which will relate to the population of interest. The data for baseline measure come from UK registry data (Hospital Episode Statistics).
- All available evidence – the model will use multiple sources of evidence and synthesise them in accordance with the principles of evidence-based medicines. This includes a systematic literature review of randomised controlled studies with meta-analysis and other high-quality evidence.
- Time horizon – the PhD will explore the lifetime cost-effectiveness of CMR.

3. **Healthcare professionals delivering intervention**

   The PhD will address the gap in the literature by looking at different healthcare professionals delivering the CMR intervention.

1.4.2 CMR complexity is not part of the available evaluations and there is limited understanding of how CMR is delivered in hospitals

Methods used for economic evaluations may have limitations when it comes to evaluating complex interventions (more information in section 1.3.2.4 ‘Economic evaluation of complex interventions’). Only limited methodological research has been done in this area, but health economists have proposed that in order to address some of these limitations, economic evaluations of complex interventions need to take special account of six central issues relating to complexity: (1) type of evaluation and valuing outcomes (2) comparators (3) perspective (4) effectiveness (5) resource use and costs and (6) modelling (Husereau *et al*., 2014). Health economic studies of CMR rarely include aspects of complexity in the evaluations. The effectiveness studies which the economic evaluations are based on often treat complexity of CMR as a ‘black box’ and rarely include aspects such as the context in which the intervention is delivered and behavioural factors.

Effectiveness studies of CMR do not often focus on how the CMR intervention works in practice (Christensen & Lundh, 2013, 2016; Hohl *et al*., 2015). Instead, they look only at the final outcome (mostly single dimensional) chosen by a researcher as clinically important and whether improvement was achieved. Most of the studies that evaluate effectiveness of CMR look at health outcomes such as mortality and readmissions. These are important outcomes to achieve, but, as mentioned by many authors of systematic reviews, a statistically significant difference for these health outcomes is rarely observed, as the studies have too short a follow-up for CMR to impact these outcomes. Outcomes from effectiveness studies such as reduction in emergency department contacts or reduction in potentially inappropriate prescribing are significantly improved by CMR, yet they are rarely used as a vehicle to evaluate the economic impact of CMR. There could potentially be more benefits associated with CMR, but there is a lack of studies that explore in-depth how CMR is applied in

a hospital setting and how it impacts on the patterns of prescribing and overall polypharmacy burden.

This PhD addresses the gap in the literature in chapters 2 and 3. Chapter 2 explores how complexity of CMR influences its economic evaluation; chapter 3 looks at outcomes of a quality improvement initiative for a hospital-based CMR and describes the effect of CMR on patterns of prescriptions and overall polypharmacy burden.

1.4.3 Which population of hospitalised patients should receive comprehensive medication review?

Different guidelines use different criteria to recommend a target group of patients which should receive CMR, but in all the guidelines the target groups share common characteristics. The common characteristics amongst all the target populations from each guideline are: older patients, patients on polypharmacy and patients with chronic or long-term conditions (Duerden *et al*., 2013; NHS Scotland, The Model of Care Polypharmacy Working Group & Quality and Efficiency Support Team Scottish Government Health and Social Care Directorates, 2012; NICE, 2015a; Scottish Government Model of Care Polypharmacy Working Group, 2015; Scottish Government Polypharmacy Model of Care Group, 2018).

Because these characteristics are shared by most patients that attend UK hospitals, there is difficulty in conducting a robust economic evaluation for a long timeframe for that broad group of patients. This might be the reason for the existing gap in literature of determining the cost-effectiveness of CMR over a lifetime time horizon by applying decision analytic modelling.

The PhD addresses the gap in the literature by determining which target population of patients should receive CMR (chapter 5). The economic analysis was conducted for a general population of elderly in a 12-month time horizon in accordance with the NICE guidelines (chapter 4) and long-term cost-effectiveness analysis was conducted for the target population identified in chapter 5, which is heart failure patients.

1.5 Aim and research questions

The identified gaps in the literature and rationale for doing research on the economic impact of CMR have led to development of the overall aim of the PhD:

This PhD aims to investigate the cost-effectiveness of comprehensive medication review in the context of UK NHS hospitals.

Subsequently, five research questions are developed to help achieve the aim:

1. In what way does CMR qualify as a complex healthcare intervention? How does complexity of CMR influence the evaluation of its cost-effectiveness?
2. How is CMR applied in inpatient hospital settings and what is the impact on prescribing patterns and costs?
3. Is CMR a cost-effective intervention for the general population of elderly acutely hospitalised patients, over a short-term (12-month) time horizon, compared with usual care, from the perspective of the UK NHS?
4. What are the target populations of patients acutely admitted to hospital who could benefit from CMR? Out of those, which population should be included in the modelling of long-term cost-effectiveness of CMR?
5. Is CMR a cost-effective intervention over a long-term (lifetime) time horizon, compared with usual care for the identified target population, from the perspective of the UK NHS and personal social services (PSS)?

1.6 The organisation of this thesis

Achieving the aim of the PhD has been planned out in seven chapters. Besides the introduction (chapter 1) and the discussion (chapter 7), each chapter represents a separate study with its own background section, methods, results, discussion and conclusions. However, all the studies are connected by the same narrative and each study influences the approach used in the next study. Each study answers one of the five research questions mentioned above and jointly all studies address the aim of the PhD. Below, I present the overview of all the chapters in the PhD:

Chapter 1: Introduction

The first chapter presents the research problem, indicates why it is important to explore whether CMR provides value for money, describes all types of medication reviews and describes the rationale for doing economic analysis in healthcare. The chapter also presents the gaps in the literature that will be addressed by fulfilling the aim of the PhD.

Chapter 2: Complexity of comprehensive medication review

The second chapter explores how complexity and context might influence the effectiveness and cost-effectiveness of CMR. The study presents the challenges of conducting an economic evaluation of complex interventions with a CMR as a case study. Exploring the literature about current economic evidence on CMR and economic evaluations of complex interventions helps to guide what approaches will be used to evaluate the economic impact of CMR in the thesis.

Chapter 3: Analysis of the application of comprehensive medication review to older patients in five inpatient hospital settings

The third chapter aims to understand the difference between CMR and usual care in terms of overall polypharmacy burden and patterns of prescribing (number of medicines deprescribed or held and new medicines started). The analysis was based on data from a quality improvement initiative carried out in five acute hospitals in North West London. The study also looks at the impact of deprescribing potentially inappropriate medicines on the average cost of medicines per patient. Data about the cost of medicines were subsequently used in modelling the cost-effectiveness of CMR in chapter 6.

Chapter 4: Short-term cost-effectiveness of comprehensive medication review

The study explores the value for money of CMR compared with usual care for the general population of elderly patients from the perspective of the UK NHS. The study was designed as a cost-effectiveness analysis with avoidance of emergency department (ED) reattendances as a measure of benefit and with costs consisting of cost of delivering CMR and costs of ED reattendances. The study informs decisions

relating to prioritisation of further research by recommending narrowing down the target population and developing a long-term economic model for that population.

Chapter 5: Target population for cost-effectiveness analysis of comprehensive medication review

Chapter 5 was created based on recommendations from chapter 4 and current gaps in the literature. The chapter uses key criteria about problematic polypharmacy and the public health importance of medical conditions to identify target populations of patients that should receive CMR. Based on the criteria, one target population is selected for the long-term analysis of the economic impact of CMR.

Chapter 6: Long-term cost-effectiveness of comprehensive medication review

The study aims to estimate the cost-utility of CMR compared with usual care for a target population (identified in chapter 5) over a lifetime horizon. The chapter uses a combination of the decision tree model and the Markov model to establish the incremental cost-effectiveness ratio, based on QALY gain from CMR and costs. Chapter 6 draws upon all the other chapters to answer the main aim of the PhD.

Chapter 7: Discussion and conclusions

In the chapter I discuss the main findings and provide answers to the research questions set in the introduction. I discuss the implications of the PhD on policy and practice and recommend areas that require further research. The chapter provides an overview of the key learnings and the limitations of the thesis.

CHAPTER 2 COMPLEXITY OF COMPREHENSIVE MEDICATION REVIEW

The main purpose of this chapter is to answer research question number 1:

In what way does CMR qualify as a complex healthcare intervention? How does complexity of CMR influence the evaluation of its cost-effectiveness?

The chapter starts by providing background about complexity of healthcare. It describes what complex interventions are and how they are delivered in complex systems. Next, the methods used in the study are described; the study used a scoping review and thematic analysis to answer the research question. The results section has two parts: part one explains why CMR is a complex healthcare intervention and part two describes how complexity of CMR impacts on six aspects of economic evaluation (type of evaluation and valuing outcomes, comparators, perspective, effectiveness, resource use and costs and modelling) (Husereau *et al*., 2014). Finally, the discussion presents the contribution of the study to current knowledge, the strength and limitations and future research directions.

2.1 Complexity in healthcare

2.1.1 Complex health interventions

The concept of complex interventions is relatively new and definitions of complex interventions vary in the literature.

Between 2000 and 2018 the Medical Research Council (MRC) developed a series of guidelines on evaluation of complex interventions (Craig *et al*., 2006, 2018; MRC, 2000). The MRC defined a complex intervention as an intervention containing several interacting components. The most recent guideline (Craig *et al*., 2018) presents the dimensions of complexity which determine what makes an intervention complex:

- Complex interactions between the components of interventions,
- Complexity relating to different numbers and range of outcomes,
- Behavioural factors that impact on the complexity of the intervention,

- Complexity related to flexibility or tailoring of the intervention,
- Complexity relating to the stakeholders targeted through the intervention.

Pawson *et al*. (Pawson, Greenhalgh, Harvey & Walshe, 2005) described key features of complex interventions. They suggest that complex interventions are theories that can be assumed to improve outcomes if delivered correctly, which implies that the programme theories of these interventions are crucial to the success of the intervention. Complex interventions work through active involvement of individuals, which is why the success of the intervention is dependent on behavioural factors. Implementation of complex interventions is nonlinear, which means they can go through a number of iterations before being implemented. The nonlinear nature of complex interventions can depend on human behaviour, where intervention can go through multiple iterations at different levels from a top-down approach to a bottom-up approach. Complex interventions are further adapted by local context and influenced by implementation at local level. However, they can also be borrowed by other organisations and influenced by others including different management teams. This relates to another key feature of complex interventions, that the process of implementing an intervention is often long, with multiple steps and people involved. The success or failure of a complex intervention relies on the summed-up success of all its components. Finally, complex interventions are open systems that can impact on the environment in which they are implemented, thus change the mechanisms and conditions which made them work in the first place (Pawson *et al*., 2005).

Shepperd *et al*. defined complex interventions in the field of service delivery as interventions delivered at the interface between primary and secondary care or interventions that are delivered in a new setting. Complex interventions are subject to behavioural factors where staff perform new tasks or the same tasks but in a new context (Shepperd *et al*., 2009).

Methods used for evaluations tend to treat complex interventions as ‘mysterious black boxes’ or the ‘unknown’. It is possible that not including complexity aspects of intervention in evaluations could lead to miscalculating the impact of the interventions, especially those affected by behaviours and preferences (Anderson, 2008; Oliveira, 2014).

Understanding the mechanisms of complex interventions may allow us to determine when and how these interventions work and how they can be replicated in different settings (Craig *et al*., 2006; Oliveira, 2014).

2.1.2 Complexity of the system

Even a seemingly simple intervention delivered in a system that is complex can become a complex intervention. A healthcare intervention can be simple or complicated in itself, but when delivered in a complex healthcare system both can be complex (Shiell, Hawe & Gold, 2008). Complex systems are dynamic and there are many theories of systems that would be interesting to combine with health economic evaluations to evaluate the cost-effectiveness of a healthcare intervention delivered in a complex healthcare system. This PhD focuses mainly on addressing the complexity nature of the intervention, rather than of the wider healthcare system in which it is delivered. However, the section below aims to illustrate that there are various types of complexities that influence analysed interventions.

In the field of complexity science, complexity is a property of a system rather than of an intervention itself. Plsek *et al*. defined a complex adaptive system as: 'a collection of individual agents with freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent's actions changes the context for other agents' (Plsek & Greenhalgh, 2001). Complex systems are adaptive to changes and can encompass other complex systems, which all behave in a nonlinear way (Shiell *et al*., 2008).

The NHS is a complex adaptive system, which itself consists of other complex systems including hospitals, GP practices and clinical commissioning groups, which in themselves are made of other systems like wards and departments. In healthcare organisations different individuals (healthcare professionals) work together in various contexts to deliver care for patients, who are also individuals with different preferences and needs.

Sometimes it can be difficult to distinguish between complex interventions and complex system approaches, as both share similar characteristics such as non-standardisation, impact of context, multiple interactions or multiplicity (Shiell *et al*., 2008).

The economic evaluation of complex interventions within a complex system has distinct characteristics. Firstly, the outcome measurement for interventions conducted in complex systems can be difficult as the properties of the complex system feature in the whole system and are not seen in only one part of the complex system or even in a sum of the individual parts. Examples of such outcomes include reduction of social exclusion, community empowerment and reduction of inequality, all of which are properties related to population health. Therefore, outcomes of complex system interventions should be measured at multiple levels. Secondly, changes made in complex systems are nonlinear and their effect may require time to be observed. Many studies have too short a follow-up period for the outcomes to develop. In order to evaluate interventions in complex systems you sometimes have to rely on intermediate outcomes that are assumed to produce future health benefits e.g. taxation of tobacco products, which can reduce the number of people smoking and thereby reduce the health burden associated with smoking (Shiell *et al*., 2008). I described the challenges of linking the intermediate outcomes with final health outcomes when evaluating complex interventions in section 1.3.2.4 ‘Economic evaluation of complex interventions’.

Finally, since a complex system is interconnected, the interventions in one part of the system can impact on other parts of the system and can also directly feed back on themselves. Therefore, effects of the intervention cannot be examined in isolation of changes in the broader context. Since everything is interconnected, spin-off effects can occur, where consequences of system level change can impact on costs and outcomes beyond those included in the research protocol of the study. It is also difficult to attribute causality in complex systems because complex systems are sensitive to initial conditions and minuscule differences, which is why randomisation may not reduce the bias associated with these interventions (Shiell *et al*., 2008).

2.2 Methods

In order to understand the complexity of CMR and its impact on economic evaluation a scoping review was conducted. Scoping reviews are a viable research method to examine the breadth of evidence about a particular topic (Rumrill, Fitzgerald & Merchant, 2010). This approach was the preferred method to answer the research

question as the topic is broad and the search terms too generic to conduct a systematic literature review. A scoping review allows different aspects of the complexity of medication review to be followed by using citation tracking and the snowball method to retrieve more relevant studies compared to a systematic search. To ensure a rigorous and well conducted review, I used the framework for scoping reviews developed by (Arksey & Malley, 2005) and described by (Rumrill *et al*., 2010) as good practice in conducting scoping reviews. The framework follows a five-stage process:

Step 1: Identifying research questions

The process of identifying research questions and the rationale for choosing the research questions for the review are presented in chapter 1. The identified research questions are:

1. In what way does CMR qualify as a complex healthcare intervention?
2. How does complexity of CMR influence the evaluation of its cost-effectiveness?

Step 2: Identifying relevant studies

The starting point for identifying relevant studies for the scoping review was the NICE guidance on Medicines Optimisation (NICE, 2015a). Using the same search criteria as NICE, I identified additional studies about the effectiveness and cost-effectiveness of CMR. All the relevant studies included in the scoping review are presented in chapter 1 of the PhD (section 1.2.2 ‘Effectiveness of medication review’ and 1.3.3 ‘Literature about cost-effectiveness of medication review’). Further to the search based on NICE guidance, other relevant studies were retrieved through electronic citation tracking and snowballing.

Step 3: Study selection

The studies selected in the scoping review included systematic literature reviews of effectiveness of CMR, studies of cost-effectiveness of CMR, national guidance and studies which provide in-depth description of the CMR intervention. Other inclusion criteria were: studies conducted in hospital or a long-term care setting; publication in the English language. Studies were excluded if the intervention delivered was not primarily a CMR intervention but a noncomprehensive medication review or other

pharmaceutical care intervention. Studies were also excluded if they were conducted primarily in a community setting, GP practice or any other setting outside of hospital or long-term care. The studies underwent initial abstract and title screening. Full-text screening of articles followed.

Step 4: Charting the data

In order to chart the data a thematic analysis was conducted using the Institute of Health Economics (IHE) framework that described the key challenges of conducting economic evaluation of complex interventions (Husereau *et al*., 2014). The framework presents six key aspects that researchers should give special attention to when conducting economic evaluation of complex interventions: (1) type of evaluation and valuing outcomes (2) comparators (3) perspective (4) effectiveness (5) resource use and costs and (6) modelling. Studies that were included in the scoping review were analysed through the lenses of these six themes and aspects of complexity of CMR were reported for all six themes.

Step 5: Collating, summarising and reporting the results

The results were summarised for each of the two research questions. Studies that provided an in-depth description of CMR intervention were collated and provided a summary of key characteristics of CMR that can classify it as a complex intervention. Studies which evaluated the effectiveness and cost-effectiveness of CMR were grouped together and framework analysis using the IHE criteria was used to classify the complexity of CMR in relation to economic analysis. For each of the six criteria, the standard economic evaluation approach is presented, then the challenges in relation to the six criteria when a complex intervention is evaluated are shown. Finally, specific challenges and possible ways to address them when evaluating CMR are described.

2.3 Results

Fifteen studies were included in the scoping review: three cost-effectiveness studies (Gallagher *et al*., 2016; Ghatnekar *et al*., 2013; Wallerstedt *et al*., 2012), six studies describing the CMR intervention (Bulow *et al*., 2018; Graabaek *et al*., 2015; Jubraj *et al*., 2015; Lennox *et al*., 2019; Szymanski *et al*., 2016; Ward *et al*., 2019), one

national guidance (NICE, 2015a), and five systematic literature reviews (one of the systematic reviews has been updated since the NICE guideline was published) (Christensen & Lundh, 2013, 2016; Graabaek & Kjeldsen, 2013; Hill-Taylor *et al*., 2016; Hohl *et al*., 2015).

The systematic literature reviews included a total of 40 studies that looked at effectiveness of CMR, 19 controlled trials (14 RCTs, one quasi-randomised, one before-after study and three controlled studies) and 21 descriptive studies.

The results are described in two sections: one describes why CMR should be considered a complex intervention; the second looks at how complexity of CMR impacts the evaluation of its cost-effectiveness.

2.3.1 CMR as a complex intervention

The definition of complex interventions implies that complex interventions have to have several interacting components (Craig *et al*., 2018). I identified two studies which conducted an in-depth analysis of the CMR intervention delivered in a hospital setting. One study comes from Denmark and is a systematic description of CMR procedure based on available literature and pharmaceutical expert opinion (Graabaek *et al*., 2015). The second study, conducted in the UK, defined the components of a successful quality improvement initiative aimed at delivering CMR in acute hospital care. The study was based on documentary analysis and observations of a two-year quality improvement initiative delivered in five acute care hospitals (unpublished data only (Lennox *et al*., 2019)). The study also conducted interviews, semi-structured interviews and focus groups to identify components of CMR intervention.

The Danish study identified five components of CMR intervention:

1. Clinical data collection
2. Information collection in relation to medical treatment
3. Patient interviews
4. Critical examination of patient's medicines
5. Creating recommendations for the attending physician

(Graabaek *et al*., 2015)

Each of the steps is context dependent and influenced by behavioural factors, system factors, setting, data sources available and other complexity aspects.

The UK study identified 17 components of successfully implemented CMR intervention, which were categorised under five domains:

1. Evidence base
2. Accessibility of the evidence base
3. Process of enactment
4. Dependent process
5. Dependent sociocultural issues

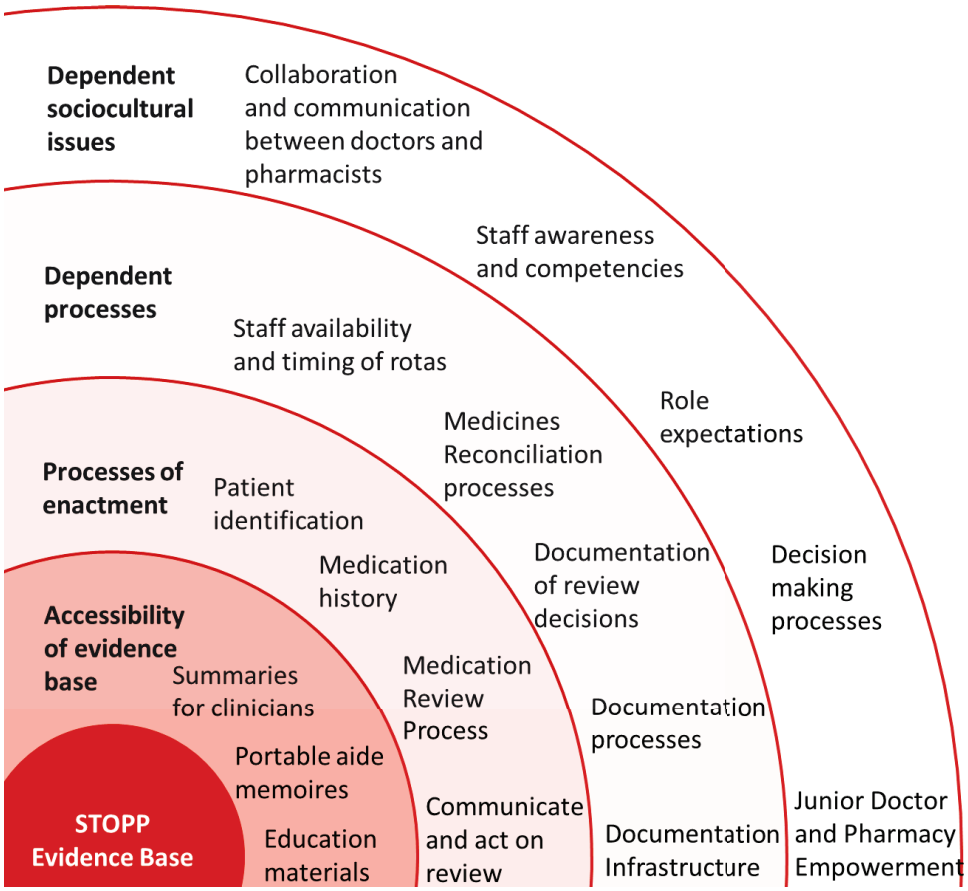
Figure 2.1 presents all 17 components of intervention within each of the five domains. The goal of the quality improvement initiative was to implement CMR conducted using a modified version of STOPP/START criteria called STOPP evidence (see chapter 6 for information on STOPP/START criteria). The figure shows the proximity of the intervention components to the evidence base. However, the authors of the study argue that although the goal was to implement STOPP evidence, the success of the CMR would not be possible without the supporting structures and the time required to put these structures in place (Lennox *et al*., 2019).

The components of the intervention are context dependent, where in some settings the intervention needs to consist of all the components and in other settings not all the components might be required. For example, a site with an established process for documenting CMR does not need to set up the documentation infrastructure as it is already in place.

Both studies show that CMR is a complex intervention with multiple interacting components. The next section will explore how complexity of CMR influences evaluation of its economic value.

Figure 2.1 Dimensions and components of implementing CMR intervention in five acute care hospitals in North West London

STOPP – screening tool of older people's prescriptions:



Source: Adapted with permission from (Lennox *et al*., 2019), see appendix D for permission letter to reproduce an extract from a third party's work.

2.3.2 Impact of complexity of CMR on the evaluation of its cost-effectiveness

First, the standard approaches to economic evaluations in relation to the six IHE criteria (Husereau *et al*., 2014) are presented, followed by the challenges of conducting economic evaluation of complex interventions in relation to the same criteria. The examples of complexity related to CMR were described for each criterion.

2.3.2.1 Type of evaluation and valuing outcomes

Health economic evaluation

Chapter 1 provided an overview of different types of economic analysis that can be used in the field of health economics. The choice of outcome determines which type of analysis is conducted. The most comprehensive analysis and the one recommended by NICE is the cost-utility analysis (CUA) (NICE, 2013b). For interventions that are aimed at prolonging life or the quality of life where the causality is straightforward, such as medicines used for treating cancer, evidence of the impact of a medicine on QALY gain can be obtained through an RCT.

Challenges with economic evaluation of complex interventions

For complex interventions a CUA may not always be possible, especially if there is challenge in expressing the benefit gained from the intervention in QALYs. This is especially difficult if the aim of the intervention is to provide other benefits aside from quality and length of life of patients (Husereau *et al*., 2014). Moreover, there could be multiple different benefits from the intervention, for example increased accessibility to the service and patient empowerment (Payne *et al*., 2013). There could also be benefits from the intervention which are probably linked to increase in quality and/or length of life, but they could be challenging to measure by QALYs. For example, it can be difficult to measure the impact of genetic services with EQ-5D (standardised questionnaire for measuring generic health status), which could not be sensitive enough to detect the impact of using testing as a diagnostic and to understand the psychological impact of the intervention (Payne *et al*., 2013).

Economic evaluation of CMR

The current literature is rich in studies that look at the effectiveness of CMR, but with different outcomes studied. Chapter 1 describes five systematic literature reviews of effectiveness of CMR done in hospital or in long-term care. The most recent studies (Christensen & Lundh, 2013, 2016) are Cochrane reviews. The first was published in 2013 and it was subsequently updated in 2016. The Cochrane review looked at the following outcomes: mortality (all-cause and due to ADE), hospital readmission (all-cause and due to ADE), hospital emergency department contacts (all-cause and due to ADE) and ADE.

The systematic literature review by (Hill-Taylor *et al*., 2016) looked at the effectiveness of CMR using the STOPP/START criteria and included studies that looked at similar outcomes to those in the Cochrane review. Additionally, the studies also looked at: quality of life; appropriateness of prescribing as measured by MAI, AOU indexes or STOPP/START criteria; length of stay in hospital; frequency of specific ADE (falls, delirium); PIP rates; clinical significance of the recommendations; functional independence measure; number of specific types of medicines; number of all medicines; number of duplicate medications; costs of medication.

The study done by (Hohl *et al*., 2015) had similar outcomes to the Cochrane study, where they examined mortality, readmissions, emergency department revisits and length of admission.

Finally, the systematic review that included the most studies (Graabaek & Kjeldsen, 2013) looked at most of the above mentioned outcomes, but in addition, looked at: satisfaction rates of physicians and patients; discrepancies in medication history; significance of interventions; overall survival; annual savings from reduction in admissions; quality of prescribing reviewed by an expert panel; prescribing problems; contact with primary healthcare; omissions and errors in prescribing; cardiac readmissions; time to readmission; and efficiency of work measures such as time needed to complete the intervention.

Most studies looked at health outcomes such as mortality or ADE; hospital utilisation (readmissions and ED visits). Studying these outcomes is important, because achieving improvement for these outcomes is the primary goal of the CMR intervention. However, the major limitation of all the studies is that they only looked at outcomes over a short follow-up period and systematic reviews conclude that treatment effects may be overlooked as it might take longer for some health outcomes to be observed. There is a need to look at the intermediate outcome in terms of the effect of CMR intervention.

Some studies look at reduction in potentially inappropriate prescribing (PIP) rates following a CMR. The impact of PIPs on morbidity and mortality is well evidenced through research using STOPP/START criteria (Gallagher, Ryan, Byrne, Kennedy & Mahony, 2008; O'Mahony *et al*., 2010; O'Mahony *et al*., 2015) or Beers criteria

(American Geriatrics Society, 2012, 2015, 2019; Fick *et al*., 2003; Lund, Steinman, Chrischilles & Kaboli, 2011). Thus, it is possible to combine evidence about the effectiveness of CMR in reducing PIPs with evidence about the negative impact of PIPs. Therefore, the reduction in PIP rates can serve as an intermediate measure of effectiveness of CMR.

2.3.2.2 Comparators

Health economic evaluation

A comparator is an intervention that the new evaluated intervention is compared against (EUnetHTA, 2015b). Comparators in the economic analysis may include, but are not limited to: medicines, medical devices, radiotherapy, healthcare procedures, counselling, combination of healthcare interventions, psychological approaches, surgery or physiotherapy (EUnetHTA, 2015a). The comparators can also include 'no intervention' or a comparator described in the literature as 'usual care/standard care/current clinical practice' (Husereau *et al*., 2013). In different settings and in different countries comparators may differ, therefore the comparator should relate to the setting in which the new intervention will be introduced (Husereau *et al*., 2013).

Using usual care as a comparator may be especially challenging as usual care might be variable with substantial differences in the usual care that patients receive for a common condition (Mant, 2008). Further, usual care can vary across different settings, different contexts and different countries.

The choice of comparator is crucial for health economic analysis as it can impact on the results of the analysis. The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) recommends listing all relevant comparators and making a choice of comparator based on criteria such as: most common, most effective, cheapest already available alternative (Husereau *et al*., 2013). The NICE guide to the methods of technology appraisal (NICE, 2013b) recommends choosing a comparator in current use in the NHS and that could be replaced by the new intervention.

Challenges with economic evaluation of complex interventions

With complex interventions it can sometimes be challenging to choose the comparator for the intervention. Choosing a comparator might not be as straightforward as when choosing a comparator for medicines, where we can compare drug A vs drug B. As the definition of complex interventions suggests, there are several interacting components of the intervention (Craig *et al*., 2018). In some cases, an intervention may already be in place in the healthcare system, but without all the interacting components being delivered appropriately, or only some parts of the intervention may be current practice. Because of these gaps in care the comparator could be the same intervention but delivered inconsistently (for example 30% of the time, instead of 100%) or it could be low-quality delivery of the same intervention.

When choosing the comparator, there could be cases where it would be appropriate to compare different components of the intervention with each other or to compare the sequence in which components are introduced. There could be a wide range of other healthcare interventions which put together could also form an appropriate comparator for the complex intervention.

Because it can be challenging to determine the appropriate comparator for complex interventions, researchers usually compare a complex intervention with no intervention or with usual care (Husereau *et al*., 2014). While usual care with a lot of health technologies can vary across different settings, with complex interventions and multiple interacting components usual care can vary not only across different settings, but even across different components of the intervention.

Economic evaluation of CMR

Table 2.1 presents the most common comparators used to evaluate effectiveness or cost-effectiveness of CMR, with usual care being the most common (16 out of 22 studies). Usually the studies did not define what usual care entails. There were two studies (Farris *et al*., 2014; O'Dell & Kucukarslan, 2005) which included noncomprehensive medication review as a comparator, one of which also used usual care as a comparator (Farris *et al*., 2014). Other comparators included: a combination of usual care and medication reconciliation in two studies (Ghatnekar *et*

al., 2013; Hellström *et al*., 2011); geriatric evaluation and management (GEM) in one study (Spinewine *et al*., 2007); and no intervention in two studies (Fertleman, Barnett & Patel, 2005; García-Gollarte, Baleriola-Júlvez, Ferrero-López, Cuenllas-Díaz & Cruz-Jentoft, 2014).

In the guideline [NG5] on Medicines Optimisation published in 2015, NICE recommends conducting CMR in the NHS (NICE, 2015a). Since the conceptualisation of medication review and later CMR, these types of interventions have been delivered across the NHS, but because CMR is a complex intervention it is delivered in various ways. Moreover, the uptake of CMR in a hospital setting is low. The quality improvement (QI) initiative described in chapter 3 showed that before conducting QI work only 4% of eligible patients admitted to five acute hospitals in North West London received CMR (Szymanski *et al*., 2016; Ward *et al*., 2019). Therefore, the appropriate comparator for cost-effectiveness analysis can be described as usual care, which entails medication review done inconsistently, low quality medication review, ad hoc medication review or noncomprehensive medication review.

Table 2.1 Comparators used in controlled studies of effectiveness and cost-effectiveness of CMR

Study	Comparator	Controlled studies included in systematic reviews			
		(Graabaek & Kjeldsen, 2013)	(Christensen & Lundh, 2016; Christensen & Lundh, 2013)	(Hohl *et al*., 2015)	(Hill-Taylor *et al*., 2016)
(Lisby *et al*., 2015; Lisby, Krogsgaard Bonnerup, *et al*., 2018)	Usual care	–	Yes	Yes	–
(Frankenthal *et al*., 2017; Frankenthal, Lerman, Kalendaryev & Lerman, 2014)	Usual care	–	–	–	Yes
(Bonnerup *et al*., 2014)	Control group (not specified)	Yes	–	–	–
(García-Gollarte *et al*., 2014)	No intervention	–	–	–	Yes
(Dalleur *et al*., 2014)	Usual care	–	Yes	–	Yes
(Farris *et al*., 2014)	(1) Noncomprehensive medication review (2) Usual care	Yes	–	–	–
(Gallagher, O'Connor & O'Mahony, 2011)	Usual care	–	Yes	–	Yes
(Hellström *et al*., 2011)	Usual care and medication reconciliation	Yes	–	–	–
(Mortimer, Emmerton & Lum, 2011)	Usual care	Yes	–	–	–
(Bladh, Ottosson, Karlsson, Klintberg & Wallerstedt, 2011)	Usual care	Yes	Yes	Yes	–

(Lisby *et al*., 2010)	Usual care	Yes	Yes	Yes	–
(Gillespie *et al*., 2009)	Usual care	Yes	Yes	Yes	–
(Makowsky, Koshman, Midodzi & Tsuyuki, 2009)	Usual care	–	–	Yes	–
(Scullin, Scott, Hogg & McElnay, 2007)	Usual care	Yes	Yes	Yes	–
(Spinewine *et al*., 2007)	Geriatric evaluation and management (GEM)	Yes	–	Yes	–
(Schnipper *et al*., 2006)	Usual care	–	Yes	–	–
(Fertleman *et al*., 2005)	No intervention	Yes	–	–	–
(O'Dell & Kucukarslan, 2005)	Noncomprehensive medication review	Yes	–	–	–
(Lipton, Bero, Bird, 1992)	Control group (not specified)	Yes	–	–	–
Economic evaluations					
(Gallagher *et al*., 2016)	Usual care	–	–	–	–
(Ghatnekar *et al*., 2013)	Usual care and medication reconciliation	–	–	–	–
(Wallerstedt *et al*., 2012)	Usual care	–	–	–	–

2.3.2.3 Perspective

Health economic evaluation

The perspective in economic evaluations is the viewpoint from which the costs and outcomes are evaluated. The evaluations can be conducted from a single or multiple perspective, such as: patient perspective, healthcare payer perspective (for example CCGs in the UK), healthcare system perspective (for example the NHS), institution perspective (for example hospital), public health perspective, social care perspective and societal perspective (these perspectives include costs associated with productivity losses) (Husereau *et al*., 2013).

The perspective used in economic evaluations is often the same for costs and outcomes, or it is only provided for costs. For the outcomes the most common perspectives described in the national guidelines on heath technology assessment are the perspective of the patient or wider societal perspective. For costs, the two most often applied perspectives are healthcare perspective and/or societal perspective (EUnetHTA, 2015b).

The NICE 'reference case' for health technology appraisal (NICE, 2013b) details that the perspectives for outcomes should include all the direct health effects for patients or other people and the perspective for costs should include all costs for the NHS and personal and social services.

But in the 'reference case', NICE suggests that if some of the technologies have benefits to other government bodies then the existence of these benefits should be identified during the scoping of an appraisal. The benefits gained to society beyond the NHS and personal social services can be included in the secondary analysis and not the reference case analysis. NICE does not include productivity costs as part of either the reference case or non-reference case analysis (NICE, 2013b).

Challenges with economic evaluation of complex interventions

Complex interventions can have long-term costs incurred and benefits experienced by many groups in society, with some of the impact hidden and not so straightforward. With the wide impact that complex interventions could have and possibly impacting a range of different stakeholders it might be difficult to capture all

the costs and benefits of the intervention, as well as all the perspectives from which the intervention should be looked at (Byford & Sefton, 2003; Husereau *et al*., 2014).

Apart from the usual healthcare and social care perspectives, the different perspectives that may be looked at also include the societal perspective, perspectives of the private and voluntary service providers, educational, criminal justice and those of patients and the public (Byford & Sefton, 2003). IHE recommends conducting secondary analyses from different perspectives to capture additional relevant costs (Husereau *et al*., 2014).

Although not included as a reference case or non-reference case analysis by NICE, in some cases, especially with public health interventions, it might be worth considering looking also at productivity losses to the economy. The economic evaluation of complex interventions from all the different perspectives can be expensive and time consuming and therefore choosing what is most important in terms of the decision problem is crucial (Byford & Sefton, 2003).

Economic evaluation of CMR

Despite NICE recommending CMR it is poorly implemented in UK hospitals (Szymanski *et al*., 2016; Ward *et al*., 2019). The success of the implementation and allocation of resources for implementing CMR is dependent on multiple stakeholders, including different healthcare professionals (pharmacists, junior doctors, senior doctors (of different specialities), nurses, pharmacy technicians, GPs, multidisciplinary teams, occupation therapists), hospital management, medicines optimisation boards, commissionaires, patients and carers (Szymanski *et al*., 2016; Ward *et al*., 2019).

Each stakeholder can impact on the success or failure of the intervention. For example, if the healthcare professional responsible for delivering CMR perceives it as not worth implementing and will not invest their time to conduct a CMR, then it is not going to be delivered. Healthcare professionals need to be convinced that their time spent on interventions provides benefit. Similarly for patients; if they see no benefit of CMR they might not implement the pharmacist's recommendations and may continue to take the medicines they had always been prescribed.

Hospital management and CCGs also need to be presented with evidence that even if it would require hiring more staff or providing incentives, delivering the intervention would still pay off in the long term.

Therefore, reporting measures of efficiency and cost-effectiveness for different perspectives could be considered. One option could be presenting local decision makers with a tool which helps establish the cost-effectiveness of CMR in their local setting based on local data (more detail in chapter 4 and 7).

2.3.2.4 Effectiveness

Health economic evaluation

Economic evaluations can be based on measures of effectiveness from a single trial, but in accordance with the rules of evidence-based medicine it is more accurate to synthesise all the available evidence (Husereau *et al*., 2013). The majority of national guidelines for health technology assessment recommend that the evidence about clinical effectiveness comes from systematic reviews of randomised control trials and meta-analyses (EUnetHTA, 2015b). The NICE 'reference case' indicates that the evidence about clinical effectiveness should be demonstrated through synthesis of evidence from all relevant and best quality studies. Therefore, the NICE 'reference case' requires that evidence comes from systematic review of evidence. Evidence from RCTs is desirable if available, however data from non-randomised trials can be included if there are no RCTs or if they provide insufficient information about the effectiveness of the intervention (NICE, 2013b).

Challenges with economic evaluation of complex interventions

Achieving desired outcomes of complex interventions is more context sensitive than when evaluating medicines or medical devices. RCTs which are the gold standard for economic evaluations are intended to look for causal relationship of the intervention. However, in doing so they strip the evaluation of context in which the intervention was delivered. Not accounting for context when evaluating complex interventions is restricting the understating of how to achieve the desired outcomes within another context (Husereau *et al*., 2014; Krauss, 2018).

Moreover, there is often a lack of extensive evidence about complex interventions. Before receiving market access, medicines require large multicentre trials; this is not the case with many complex interventions, which do not require large studies for access to the market. Researchers evaluating complex interventions may rely on single trials and non-randomised studies (which are not easily synthesised through meta-analysis) (Husereau *et al*., 2014).

Economic evaluation of CMR

Because CMR is a complex intervention it can impact on multiple outcomes (see section 2.3.3.1 about outcomes of CMR). Therefore, even though there are multiple systematic literature reviews published they include a mixture of different studies. Because context plays a key role in delivery of CMR, the studies are heterogeneous in terms of how the intervention is delivered, who delivers the intervention, which patients receive the intervention, what outcomes are measured, the follow-up time in the study, etc. Therefore, synthesis of evidence may prove challenging and although there is overlap in terms of the studies included in each of the five systematic reviews (Christensen & Lundh, 2016; Christensen & Lundh, 2013; Graabaek & Kjeldsen, 2013; Hill-Taylor *et al*., 2016; Hohl *et al*., 2015), there is not a single study which was included in all five reviews.

There are many context-related factors that can influence the effectiveness of CMR, such as systemic factors and behavioural factors (Szymanski *et al*., 2016; Ward *et al*., 2019). Systemic factors include interaction between different parts of the healthcare system, for example continuity of care and implementation of recommendation of CMR across primary care, secondary care, social and community care. Systemic factors also include availability of resources to deliver the intervention:

- Healthcare professionals capable of delivering CMR
- Time allocated for delivery of the intervention
- Training provided to reviewers
- Tools in place for high quality CMR, such as STOPP/START criteria or STOPIT, which help determine potentially inappropriate prescribing (PIP)

- Infrastructure available for communicating changes in prescriptions, for example space to put recommendations on an electronic or paper discharge summary

(Lennox *et al*., 2019; Szymanski *et al*., 2016; Ward *et al*., 2019)

Behavioural factors include the healthcare professional's experience in conducting CMRs. A study of 42 junior doctors examined their attitudes towards and awareness of medication review. Most junior doctors reported that they felt uncomfortable changing medicines without consulting senior doctors first. Junior doctors were confident about prescribing new medicines but were not confident about deprescribing medicines patients were already taking (Jubraj *et al*., 2015). Other behavioural factors include engagement of the patient, which can impact on the effectiveness of CMR, as well as communication between different healthcare professionals, where without proper communication deprescribed medicines can be re-prescribed or never even stopped (Szymanski *et al*., 2016; Ward *et al*., 2019).

2.3.2.5 Resource use and costs

Health economic evaluation

Costing consists of two processes: first, the estimation of resource use in natural units and secondly, estimating the unit costs for the resources used. The resource estimation can be based on data from clinical trials, routinely collected data, registers and other databases or other sources available in the literature. Prices can be estimated from a wide range of sources. If there are multiple sources that report different prices, the impact of different prices on the results of cost-effectiveness analysis can be tested in sensitivity analysis (Husereau *et al*., 2013).

The cost included in the analysis will depend on the perspective used. National guidelines which recommend conducting analysis from the healthcare perspective advise using direct healthcare costs, whereas guidelines which recommend the societal perspective advise also including indirect costs and costs for other sectors besides the health sector (EUnetHTA, 2015b).

The NICE 'reference case' indicates that evidence about resource use and cost should be collected systematically. For health technologies, public list prices should

be used; for medicines, drug tariffs or costs from the Electronic Marketing Information Tool should be used. Costs that are not published on list prices can be used if they are publicly available. For estimating resource use, healthcare resource groups (HRGs) can be applied, but sometimes it might be more appropriate to determine the resource use by applying other research methods such as micro-costing studies. All relevant costs related to the evaluated condition should be included in the analysis. The cost in economic evaluations should exclude value added tax (VAT) (NICE, 2013b).

Challenges with economic evaluation of complex interventions

The variation in costs and resources associated with complex interventions is the major challenge for their measurement. Complex interventions can have several interacting components and each of the components can use different resources and incur different costs (Husereau *et al*., 2014). Even one component of an intervention can vary in terms of costs and the resources required to deliver it; as the number of components to an intervention increases, so the variation in costs and resources may also increase.

Context also plays a significant role in the amount of resources used and costs incurred (Craig *et al*., 2018). For example, delivering an intervention in a large hospital with multiple wards can be different from implementing the same intervention in a smaller hospital. The healthcare professionals delivering the intervention might differ; where in one hospital it is a nurse delivering the intervention, in another hospital it is the consultant or junior doctor, and in a third hospital it is a pharmacist that is providing the service.

Complex healthcare interventions often tackle patients' complex needs, which can be case sensitive. For example, medication reconciliation can be done quickly if the patient receives only a few medicines; it will take much longer for patients with comorbidity and with polypharmacy (Karnon, Campbell & Czoski-Murray, 2009; Matza *et al*., 2015; Meguerditchian, Krotneva, Reidel, Huang & Tamblyn, 2013). Therefore, it might be challenging to properly establish the exact cost of a complex intervention. Researchers exploring complex interventions may need to develop original cost algorithms in order to establish the most accurate cost of the intervention (Husereau *et al*., 2014).

Economic evaluation of CMR

A study which developed a systematic procedure description of CMR (Graabaek *et al*., 2015) looked at 13 studies of CMR to find a description of the CMR procedure. The authors found disparity among the ways in which CMR was delivered. The disparities related to the type of tool used for the review (e.g. STOPP/START criteria or Beers criteria); screening (electronic screening or ward round); scope of the review (e.g. each CMR intervention could focus on different aspects of pharmaceutical care such as looking for drug–drug, drug–disease interactions dose adjustments, duration of treatment, costs, ADE etc) (Graabaek *et al*., 2015). All of these can impact on the resource use and cost for delivery of CMR.

In the UK, NICE recommends that the appropriate healthcare professional delivering CMR should be determined locally (NICE, 2015a). This means that in each setting a different healthcare professional may deliver the intervention. Costs vary across different healthcare professional groups, as can costs for different levels of seniority within the same group. Therefore, it might be challenging to estimate the appropriate resource use required to deliver CMR.

Even within one trial there could be variations in terms of how the intervention is delivered. For example, changes to medicines could either be communicated verbally or noted in patients' medical records (Bulow *et al*., 2018). The disparities in CMR delivery can impact on the effectiveness of the intervention and on the time needed to complete the intervention. Moreover, the age, number of medicines and complexity of the condition can all impact on the length of the intervention and thus its cost.

Therefore, it might be appropriate to account in the analysis for disparities in the length of the intervention and the healthcare professional delivering the intervention.

2.3.2.6 Modelling

Health economic evaluation

Health economic models are used for evidence synthesis and for estimating the clinical and cost-effectiveness impact of an intervention (NICE, 2013b). Exploration

of the model structures used in previous studies of the disease of interest is recommended (Husereau *et al*., 2013).

Models are needed when (1) evidence about the intervention comes from multiple studies, (2) outcomes used in the studies are intermediate outcomes and not quality and length of life or survival (3) the target population from the studies is not the same population as the one which will use the intervention once it is adopted by the NHS (4) the costs and benefits of the intervention exceed the follow-up period of the trials (5) trials did not compare the intervention with all the relevant comparators (6) trials include crossover design in which treatment is switched during the trial (NICE, 2013b).

In the introduction, different models used in decision analytic modelling are presented; this includes individual and cohort models. The choice of model is dependent on the complexity of the decision problem.

Challenges with economic evaluation of complex interventions

A more advanced approach to modelling may be required to accurately reflect different components of the complex intervention and broader spectrum of care pathways (Husereau *et al*., 2014). Innovative approaches to modelling might be used in order to better reflect the current treatment practice, disease natural history and efficacy and safety of the intervention. New approaches might be needed based on the availability of data and outcomes chosen for the analysis (Husereau *et al*., 2013). Researchers might consider using 'whole disease modelling' and using discrete event simulation models that account for the intervention and the context in which it is delivered (Husereau *et al*., 2014).

Economic evaluation of CMR

Because there is currently no cost-effectiveness analysis of hospital-delivered CMR based primarily on decision analytic modelling and evidence synthesis, health economic modelling for CMR requires development of new cost-effectiveness models. Because of the complexity of the intervention, availability of data and outcomes which are connected to the effectiveness of the intervention, innovative approaches might be required such as linking evidence about the intermediate effect of CMR with the final patient outcome. This would entail combining two sources of

evidence: evidence about the effectiveness of CMR in reducing potentially inappropriate prescribing (PIP) and the evidence base around the disease burden and mortality associated with PIP.

2.4 Discussion

2.4.1 Contribution to the field

Understanding the complexity of CMR is crucial for appropriate evaluation of its effectiveness and cost-effectiveness. Most studies evaluating CMR do not include aspects of complexity of the intervention, which is potentially a major reason why there is conflicting evidence about clinical and economic effects of CMR. To my knowledge, this is the first literature review about complexity of CMR and its impact on economic evaluations. Table 2.2 summarises the key recommendations and considerations for economic evaluations of CMR based on the scoping review of literature around existing evaluations of CMR.

Table 2.2 Comparison of differences in gold standard health economic evaluations and economic evaluation of CMR

	Standard health economic approach	Economic evaluation of CMR
Type of evaluation and valuing outcomes	The gold standard for economic evaluation of health interventions in the UK is cost-utility analysis, where QALY gain is the measure of health benefit.	Because of the short time horizon in studies evaluating CMR it is not always possible to observe the benefits in terms of QALY gain within the timeframe of the studies. However, studies have shown effectiveness of CMR in terms of intermediate outcomes such as reduction in emergency department admissions or potentially inappropriate prescribing. Moreover, CMR impacts on outcomes other than just patient health outcomes, such as staff engagement, accessibility or patient engagement.
Comparators	Alternative intervention	CMR is already in place in the UK, however its consistency and quality could be improved. Therefore, the comparator of CMR can be a CMR done inconstantly, low quality CMR, ad hoc medication review or noncomprehensive medication review.

Perspective	NHS and personal social services (PSS)	Broader perspective that includes benefits and costs for different stakeholders
Effectiveness	The gold standards for evaluating effectiveness of an intervention are systematic reviews and randomised control trials. They rarely account for the context in which the intervention is delivered.	Context is a critical determining factor in the success of an intervention. When CMRs are spread to new settings, they may fail to achieve the same impact as in RCTs. This may limit the generalisability of results. There are many variables likely to influence effectiveness of medication review: a) Systemic factors (resources in place; time available; interaction between different parts of the healthcare system) b) Behavioural factors (experience of the healthcare professional; engagement of the patient; communication between different healthcare professionals).
Resource use and costs	Cost and resources quantifiable	Resources used for delivery of CMR can be very variable across different organisational and financial settings and different populations of patients receiving the intervention. Therefore, the main resource for delivery of CMR (time of healthcare professional to complete CMR) is case sensitive. It is important to account for variation in delivery of CMR across different settings and in different contexts.
Modelling	Long-term outcomes e.g. mortality, QALYs	Results from studies might not reflect long-term outcomes. We assume that the final outcomes can be estimated based on intermediate outcomes.

2.4.2 Contribution to thesis and implication for further research

The scoping review addressed the gap in literature identified in chapter 1 by providing an overview of the complexity of CMR and the impact on economic evaluation. The study from this chapter contributed to the overall PhD thesis by providing recommendations on how to approach economic modelling of CMR. The recommendations presented in table 2.2 were implemented in two cost-effectiveness analyses conducted as part of this PhD – one in chapter 4 and one in chapter 6.

The study has three implications for future research. Firstly, it highlights the importance of accounting for context and complexity when evaluating the effectiveness of CMR. Treating CMR as a simple intervention, the effects of which could be easily measured through randomised control trials, has so far provided conflicting results. Future studies should consider what type of medication review they evaluate and how different components of the intervention interact with each other. Does the hospital in which the intervention is delivered have sufficient resources (healthcare professionals' time, adequate medicines reconciliation procedure, documentation infrastructure, etc.) and experience to deliver good quality CMR interventions or should the hospital first invest in an implementation strategy and training before conducting evaluation of the effectiveness of CMR?

Secondly, looking at the challenges in evaluation of complex interventions, using CMR as an example can serve as a case study for future research. Researchers can look at other complex interventions and try to 'unpack the mysterious black box' to see how complex interventions work and how they can be evaluated. The study from this chapter is the first research which gives special consideration to the six aspects of complexity described by IHE that require special attention when doing economic evaluation of complex interventions.

Finally, the study provides recommendations for conducting economic evaluation of CMR, which I implemented as part of this PhD.

2.4.3 Strengths and limitations

The study is the first review to examine the complexity of CMR and the implications for establishing the value for money of the intervention. The study provides an overview of the challenges that face researchers when conducting economic evaluation of complex interventions and gives examples of challenges specific to CMR. The study provides recommendations on how some of the challenges related to cost-effectiveness analysis of CMR can be addressed.

The study was a scoping review and not a systematic review, which is associated with limitations. There is potential for publication bias, which means that depending on the search strategy some relevant evidence could be excluded from the analysis. However, because the search strategy was designed to include all the relevant

systematic literature reviews of RCTs and controlled studies, cost-effectiveness analysis and UK national guidance, the studies with the highest level of evidence according to the principles of evidence based medicine (EBM) were included in the review (Swanson, Schmitz & Chung, 2010).

2.5 Conclusions

CMR is a complex system intervention because it has several interacting components. Two studies presented an in-depth description of CMR (Graabaek *et al*., 2015; Lennox *et al*., 2019) and identified five and 17 interacting components respectively. The successful delivery of CMR is dependent on all the components of the intervention and the context within which the intervention is delivered. For example, without one component (good quality clinical data) available it might not be possible to deliver CMR. Even if you have good quality data but another component is missing e.g. there is no available healthcare professional to deliver the intervention (because of other work commitments) the intervention might fail. Also, after reviewing a patient's medicines another component of CMR is crucial; for CMR to be sustained there needs to be good communication between different parts of the healthcare system to assure continuity of care. Therefore, the CMR needs to be properly recorded and the reason for modifying the medication regime must be communicated with the GP and community and social care.

Complex system interventions like CMR are difficult to evaluate given the scope and number of factors to consider. When evaluating these interventions, the standard health economic approach may not fully capture the complexity of the intervention. Therefore, economic evaluations of CMR should try to accommodate the context and complexity of the intervention.

CHAPTER 3 ANALYSIS OF APPLICATION OF COMPREHENSIVE MEDICATION REVIEW TO OLDER PATIENTS IN FIVE INPATIENT HOSPITAL SETTINGS

Chapter number 3 is an in-depth analysis of CMR intervention, with the main purpose of answering research question number 2 of the PhD:

How is CMR applied in inpatient hospital settings and what is the impact on prescribing patterns and costs?

In order to answer the research question, data from the Review of Medicines in Acute Care (ReMAC) initiative were analysed. ReMAC was a quality improvement initiative that aimed to improve medicines optimisation for older patients by optimising the delivery of medication review (Szymanski *et al*., 2016; Ward *et al*., 2019). The chapter begins with introducing the ReMAC initiative, the rationale for the initiative, its aim and how it was created. The methods used in ReMAC and all the implementation activities undertaken as part of it are presented. The chapter also highlights the outcome measures used in ReMAC and presents the main findings relating to prescribing patterns and costs of patients receiving CMR compared to patients receiving usual pharmaceutical care.

The methods used in the analysis are presented, with the description of data sources used for the analysis (British National Formulary – BNF and data from ReMAC initiative). Then the definitions of outcome measures analysed and the methods used for costings of medicines and statistical data analysis are presented.

The results focus on comparing CMR with usual care in terms of impact on prescribing patterns, impact on cost of medicines and impact on the overall polypharmacy burden. The section consists of four analyses: (1) analysis of characteristics of the study population; (2) comparison of CMR and usual care in terms of changes in prescribing patterns; (3) comparison of CMR and usual care in terms of cost of medicines; (4) analysis of the impact of CMR, age and gender on the difference in number of medicines.

The discussion focuses on the contribution of the study to wider knowledge about patterns of prescribing and cost of deprescribed medicines following a CMR and the interaction effect of CMR, gender and age on number of medicines. Suggestions for future research are presented along with the strengths and limitations of the study. The conclusion focusses on presenting the answer to the research question and the summary of the findings.

3.1 Background

As described in chapter 2, most of the studies of effectiveness of CMR look at health outcomes such as mortality, ADE, hospital utilisation and prescribing quality (Christensen & Lundh, 2016; Christensen & Lundh, 2013; Graabaek & Kjeldsen, 2013; Hill-Taylor *et al*., 2016; Hohl *et al*., 2015). The primary aim of CMR is to achieve improvement in these outcomes, but due to a short follow-up period in most studies it is not always possible to observe these improvements and therefore significant treatment effects may be overlooked. A recommendation from chapter 2 was to investigate further using intermediate outcomes, such as reduction in PIP rate, as a vehicle to understanding how the final outcome is achieved. A number of intermediate outcome measures exist which have not yet been studied by researchers, such us prescribing patterns measured by the number of medicines deprescribed, held and started. Research into the impact of CMR on prescribing patterns helps us understand the mechanisms of the intervention to understand not only whether the final outcome was achieved, but also how it was achieved. Focusing on all the medicines and not just the ones that are potentially inappropriate can provide better understanding of the impact of CMR on the overall polypharmacy burden. Looking in greater depth at patterns of prescribing can also enable us to understand how the cost of prescribing changes after CMR and how it compares to the cost of prescribing for usual care patients. This information is unavailable in the published literature.

Three studies that were included in the systematic literature reviews of effectiveness of CMR (more information in chapter 1) looked at cost of medicines as an outcome measure (Fertleman *et al*., 2005; Frankenthal *et al*., 2014; Gallagher *et al*., 2011). A subsequent update of the Frankenthal *et al*. study (Frankenthal *et al*., 2017) was also

included. The studies provided only the estimate of the overall prescribing cost change, rather than change based on patterns of prescribing. Additionally, the sample size in the studies did not exceed 400 patients and hence a larger sample size is needed to increase the generalisability of the results. This chapter aims to address that gap in the literature by providing an insight into the effect of CMR on the overall polypharmacy burden, as well as the number of medicines stopped, started and held following a CMR intervention. Subsequently this chapter aims to understand the costs of these medicines, by looking at a larger sample size of patients than currently published.

3.1.1 Overview of the ReMAC study

In order to achieve that aim, I will analyse data collected as part of a quality improvement initiative called ReMAC. In September 2014, researchers from Chelsea and Westminster Hospital in London undertook a quality improvement (QI) initiative with the support of the National Institute for Health Research's Collaborations for Leadership in Applied Health Research and Care North West London (NIHR CLAHRC NWL). The initiative used NIHR CLAHRC NWL's systematic approach (Reed, Howe, Doyle & Bell, 2018) to deliver the improvement and associated implementation activities. The aim of ReMAC was: "to improve medicines optimisation for older patients in North West London hospitals using a breakthrough collaborative approach to embed patient-centred medication reviews into routine practice in acute care" (Ward *et al*., 2019).

The initiative focused on optimising the process for reviewing prescribing by improving the quality and consistency of delivering medication review for older patients in acute care. The process included improvements in transitions of care, by optimising documentation and communication of medication review findings and transferring them to community care. The initiative and all implementation activities were co-designed by pharmacists, patients, doctors and improvement scientists. ReMAC improved the targeting and flagging of inappropriate prescriptions, resulting in an increased number of medication reviews being delivered with an emphasis on encouraging patients to be involved in the medication reviews (Ward *et al*., 2019).

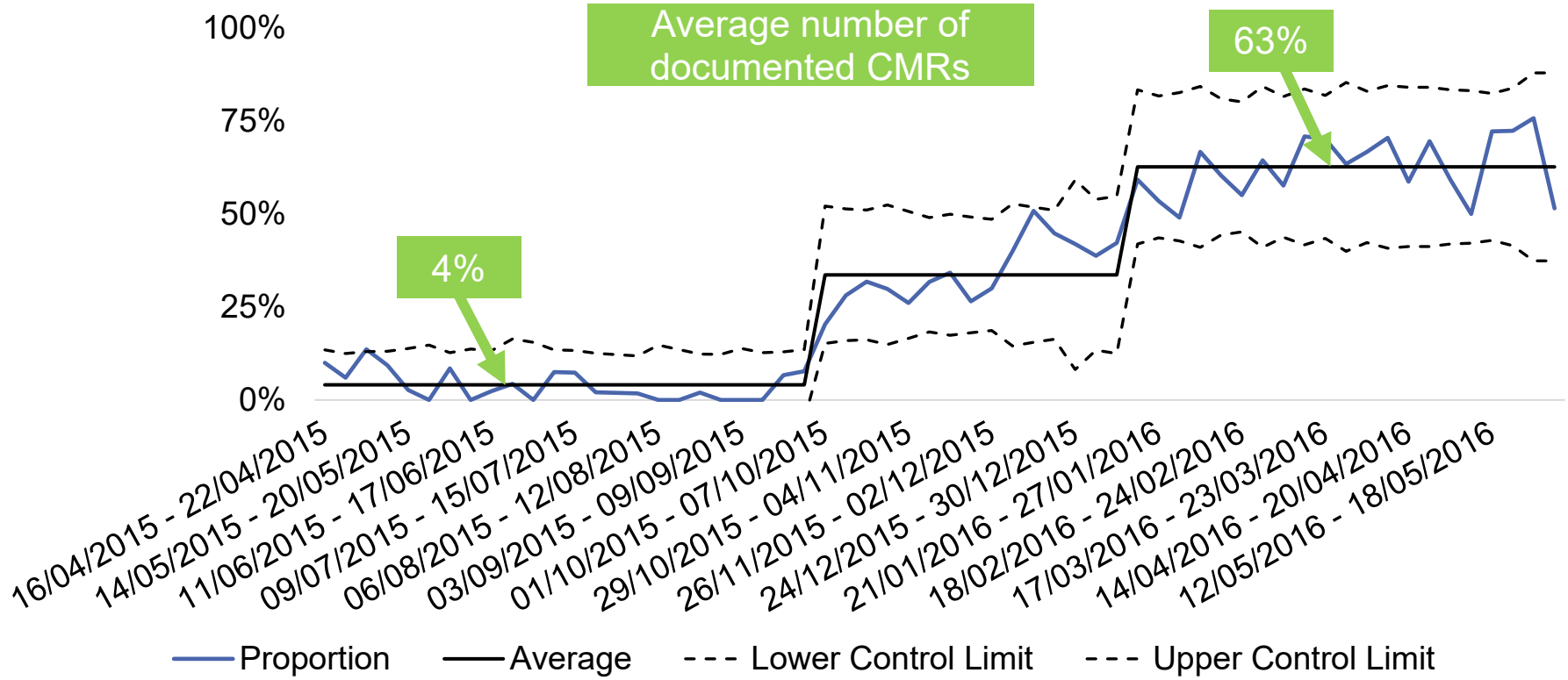
The ‘breakthrough collaborative’ involved five acute hospitals in North West London. The methods used to design and implement the intervention were developed in line with the principles of Successful Healthcare Improvements From Translating Evidence in complex systems (SHIFT-Evidence) framework (Reed *et al*., 2018), summarised by three principles: ‘act scientifically and pragmatically’; ‘embrace complexity’; and ‘engage and empower’ (Reed, Howe, Doyle & Bell, 2019). The core components that lead to an increase in the number of medication reviews conducted included:

- QI training for all team members with regular meetings to discuss the progress. Training included the development of skills and the use of QI tools (e.g. action effect diagrams, plan-do-study-act cycles, process mapping, stakeholder engagement, patient and public engagement and involvement, measurement for improvement).
- Development of tools that are intervention specific and facilitate conducting medication review.
- Education of pharmacists and other healthcare professionals on wards on how to properly conduct medication review.
- Changes to documentation and electronic systems for ease of documentation of medication review.

The study conducted an analysis of discharge summaries (DSUM) and patients’ notes to measure the effectiveness of the intervention. Data collection was run between 2015 and 2016, and the data were collected for 3,043 patients (Ward *et al*., 2019).

The main outcome measure in the study was the percentage of DSUMs with documented medication review. Improvements in the percentage of documented medication reviews were recorded for all five sites with the scale of change varying across sites. For all sites, the average percentage of reported medication reviews increased from 4% before the implementation of quality improvement activities to 63% by the end of the QI initiative. The P-charts (figure 3.1) show the improvement in percentage of documented medication reviews (Ward *et al*., 2019).

Figure 3.1 Number of documented medication reviews before and after intervention aimed at improving the quality and consistency of medication reviews



Source: Figure calculated based on data from (Ward *et al*., 2019), unpublished data.

3.2 Methods

3.2.1 Research hypotheses

There were four different statistical analyses conducted as part of this chapter to compare patients who received CMR with patients who received usual care.

Analysis 1 – looked at participant demographics and general characteristics using descriptive statistics.

Analysis 2 – used a t-test to compare the means of the number of medicines deprescribed, held, and started for the CMR and usual care groups. The analysis tested the null hypothesis that:

I. Receiving a CMR has no effect on the mean number of medicines:
   a. Deprescribed
   b. Held
   c. Started

Analysis 3 – compared mean cost per patient of the deprescribed medicines between the CMR and usual care groups, using the t-test and testing the following hypothesis:

II. Receiving a CMR has no effect on the mean cost-savings per patient from deprescribing medicines.

Analysis 4 – three-way ANOVA (2x2x5) was conducted to see whether there was an interaction effect between three independent variables – gender, age and CMR – and the dependant variable of the difference between the number of medicines on discharge and the number of medicines on admission. Three-way ANOVA tests seven null hypotheses; three hypotheses tested the main effect of each independent variable on the dependant variables:

III. Receiving a CMR has no effect on the difference between the number of medicines on discharge and admission.
IV. On average, the difference between the number of medicines on discharge and admission is the same for all age groups.

V. On average, the difference between the number of medicines on discharge and admission is the same for males and females.

Three null hypotheses tested two-way interactions:

VI. There is no interaction effect between CMR and age in terms of the difference between the number of medicines on discharge and admission.

VII. There is no interaction effect between CMR and gender in terms of the difference between the number of medicines on discharge and admission.

VIII. There is no interaction effect between age and gender in terms of the difference between the number of medicines on discharge and admission.

One null hypothesis tested a three-way interaction:

IX. There is no three-way interaction effect between all three factors (gender, age and CMR) in terms of the difference between the number of medicines on discharge and admission.

3.2.2 Data source

The methods section presents two data sources that were used in this chapter: the data collected in ReMAC and the British National Formulary (for the cost data). The main characteristics of the ReMAC study are presented below.

Review of Medicines in Acute Care (ReMAC)

Study design

ReMAC was a prospective, multicentre, nonrandomised 'breakthrough collaborative' quality improvement initiative. The study was scaled up in one site and rolled out to four other sites. The initiative took place at five acute teaching hospitals within North West London and the data collection was carried out between 16 April 2015 and 2 July 2016.

Ethics

The ReMAC initiative met the criteria for operational improvement activities and therefore according to the research policy of the Chelsea and Westminster Hospital NHS Foundation Trust (CWH) it was exempt from ethics review. Ethics approval was not required for this study, as the ReMAC initiative was part of service evaluation and improvement activity and not human subjects research. An ethics waiver was

granted by the research and development lead of CWH. Furthermore, the analysis conducted in chapter 3 was approved by the NHS Health Research Authority (IRAS 188851) as part of a larger research application of NIHR CLAHRC NWL (see appendix C for protocol and approval).

Data collection

To evaluate the effectiveness of the 'breakthrough collaborative' in the delivery of medication review, a retrospective analysis of the DSUMs and patients' notes was conducted in order to find documented evidence of medication review. The analysis was first carried out at baseline before implementing the quality improvement initiative. Following that, prospective data were collected for the duration of the study. Data were analysed using the statistical process control (SPC) method, which is often defined as a set of analytical techniques for plotting data over time (Mohammed, 2004). The results are presented in figure 3.1.

Patients

The study included patients aged ≥ 70 years old admitted to one of the five hospital sites. Four of the sites collected data from care of the elderly wards and one site collected a random sample of 20 patient notes per week from all wards, including medical, surgical, elective and non-elective wards. There were three exclusion criteria: (1) death of patient before discharge, (2) short admission or attendance at the ward (< than 24 hours), (3) in sites which carried the study only on the care of the elderly wards, the exclusion criterion was also admission to another ward.

British National Formulary (BNF)

To analyse the costs, dosage regimen and duration of treatment of the deprescribed, held and started medicines, analysis in this chapter utilised the BNF website (www.medicinescomplete.com, last update 27 June 2019). BNF is the reference book for pharmaceuticals used in the UK NHS. The BNF provides information about medicines, their prescribing, pharmacology, names, indication of use, doses, legal classification, availability of generics, adverse events and costs (BNF, 2019).

3.2.3 Definitions of outcome measures

The main outcome measure in the ReMAC study was the percentage of DSUMs with documented medication review. The ReMAC study defined two types of medication review in acute care that were included in the analysis:

Comprehensive medication review

A comprehensive medication review was defined as "a structured critical examination of all current medication with the objective of reaching an agreement with the patient about treatment. The reviewer systematically considers the merits and risks of different medications, stops inappropriate medicines and starts others optimising their impact, minimising the number of medication related problems and reducing waste. The 'reviewer' should be a senior clinician working with the patient or carer" (Szymanski *et al*., 2016; Ward *et al*., 2019).

Interim medication review

"An interim review occurs when a patient presents acutely unwell or when a long-term condition deteriorates or improves. In the acute hospital setting, interim reviews leading to short-term changes frequently take place." (Szymanski *et al*., 2016; Ward *et al*., 2019).

The outcome measure (documented medication review) consisted both of the interim and the comprehensive medication review. The review was only included if it was documented either in the DSUM or in patients' notes. For the purpose of consistency with the rest of the PhD, the documented medication review will be referred to as comprehensive medication review (CMR).

Other data collected in the ReMAC included:

- Patients' demographic data (age and gender)
- Information relating to hospital admission (date and hospital to which the patient was admitted)
- Number of medications on admission
- Number of medications on discharge
- Were there any changes to medicines recorded in the DSUM or patient's notes?

- Number of patient review notes
- Was the patient counselled about the changes to medications?
- Number of medications deprescribed
- Number of medicines held (because they are considered ‘non-essential’ or currently ‘unnecessary’ or contributing to morbidity) pending further medication review
- Number of new medicines started
- The names and doses of medicines that were stopped or started

Difference in prescribing pattern

I analysed three outcomes related to the prescribing patterns: number of medicines deprescribed, number of medicines held and number of medicines started (research hypothesis I). The outcomes were tested using the t-test to compare whether the mean value (of deprescribed, held, started medicines) was statistically different between CMR and usual care groups.

Difference in cost of medicines

Another outcome measure was the cost of deprescribed medicines. To compare the mean cost of deprescribed medicines for CMR versus usual care groups (hypothesis II) the outcomes were tested using a t-test to compare whether the mean value was statistically different between CMR and usual care groups.

Difference in number of medicines

I analysed the difference between the number of medicines on discharge and the number on admission. This incremental difference in this chapter will be referred to as ‘the difference in number of medicines’. To test null hypotheses for this outcome (hypotheses III-IX) three-way ANOVA was used to see whether age, gender, CMR or a combination of these variables affects the difference between the number of medicines on discharge and on admission. Three-way ANOVA was the preferred statistical method as it can test whether there was a main effect of each of the variables on the difference in the number of medicines, but also whether an interaction between these variables affected the difference in the number of medicines.

3.2.4 Costing

Cost value was attached to each of the 10,856 deprescribed or started medicines by manually searching the British National Formulary (BNF) website for data on cost and standard daily dose.

The costs extracted from BNF were based on the drug tariff prices, which include hospital prescribing (dispensed in hospital pharmacy and in the community) and primary care prescribing dispensed in the community. The drug tariffs are based on the net ingredient cost, which includes the basic price of a drug excluding VAT and the amount paid to contractors for NHS services (cost of medicines and appliances supplied against an NHS prescription form) and remuneration (professional fees and/or allowances paid as part of the NHS pharmacy contract) (PSNC, 2019). The costs do not include NHS negotiated discounts, nor do they include patients' co-payments costs (NHS Digital, 2018c).

Where there was enough information in the data collected by the ReMAC study about dosage regimen, duration of treatment and the brand name of the product, these were used to calculate the costs. There were cases where only the name of the medicine was provided with no additional information. For this type of data on medicines, the BNF costs were used to estimate the potential standard monthly cost of treatment with each medicine group. The cost of medicines was based on the lowest BNF cost option. The following formula was used to calculate the monthly cost of treatment:

$$Monthly\ cost\ of\ medicine\ A = \left(\frac{Drug\ tariff\ price}{Number\ of\ units\ x\ \frac{Dose\ in\ 1\ unit}{SDD}} \right) x\ 30 \qquad (3.1)$$

Units - tablets, capsules, ampoules etc; SDD – standard daily dose

3.2.5 Data analysis

Statistical analysis was conducted using the SPSS (Version 25, IBM Corp.) software. Population characteristics were initially explored using descriptive statistics (see table 3.1)

Analytical considerations

The planned statistical tests mentioned above are all parametric tests. To conduct parametric tests, the data should typically be normally distributed. A detailed description of the four basic normal distribution assumptions is beyond the scope of this work (see (Field, 2009) for further details on the matter). To test for normality, researchers use tests of normality such as Normal Q-Q plots, Shapiro-Wilk, Kolmogorov-Smirnov, etc. In this chapter, parametric tests were conducted without testing for normality in the data. This exception was based on the 'central limit theorem', which details that, if the sampling is based on 30 or more observations, the sampling distribution of the mean can be assumed to be normal. The sample size of the data used in this chapter was n = 3,043. For this reason, normality was assumed and not tested. Lane *et al.* explains that 'Given a population with a finite mean μ and a finite non-zero variance σ2, the sampling distribution of the mean approaches a normal distribution with a mean of μ and a variance of σ2/N as N, the sample size, increases' (Lane *et al*., 2019).

For all the tests conducted, the appropriate assumptions of homogeneity of variances were checked to make sure that the appropriate tests were disseminated. Four independent sample t-tests were conducted to compare the difference between CMR and usual care in the number of started medicines, number of held medicines, number of deprescribed medicines and costs of deprescribed medicines (test for hypotheses I and II). Please note that for these tests a Bonferroni corrected α of 0.0125 (0.05/4 independent tests) is reported rather than the standard significance level of 0.05. This was carried out as a measure for minimising Type 1 errors.

A statistical analysis was conducted to determine the effect of CMR on the difference between medicines on discharge and medicines on admission (test for hypotheses III-IX). The difference in medicines could possibly be dependent on the gender and age of patients. Therefore, analysis focused on whether a three-way interaction

effect exists and if it explains the difference in the number of medicines. A three-way ANOVA (2x2x5) was conducted to determine whether there is an interaction effect between three independent variables: receiving CMR intervention (two levels: yes or no), gender (two levels: male or female) and age (five levels: 70-74; 75-79; 80-84; 85-89; ≥ 90); on a continuous dependent variable (i.e. if a three-way interaction exists on the difference in number of medicines). To do this, I ran a three-way independent ANOVA looking at the main effects of each of the independent variables (age, gender, CMR) as well as the possible interaction effect of these variables on the difference in number of medicines. Three-way ANOVA allows to look at both the interaction effects and the main effects, which is why this method was chosen for the analysis. All values were presented as mean values, with standard error 95% CI and p-values of ≤ 0.05 were considered statistically significant.

Missing data

To handle missing data (for all data except the cost data), I used pairwise deletion analysis, which removes all the missing observations on a case by case basis for each analysis. The decision was made based on the assumption that the variables were missing completely at random. The pairwise deletion was used to maximise all data available for each analysis.

For cost of deprescribed medicines the pairwise deletion was used to remove missing values, because cost of deprescribed medicines was well recorded (91.02% of data available) and there was no significant difference between the amount of missing data in both groups (CMR and usual care). However, the cost of started medicines was poorly recorded (38.26% of data) and there was a significant difference between the amount of data missing in the CMR and usual care group. Because there was a large amount of data missing and the data were not missing at random, the decision was made to not analyse the cost of started medicines.

3.3 Results

3.3.1 Analysis 1: Characteristics of the study population

The first part of the analysis looked at participant demographics and general characteristics (table 3.1). Data were collected for 3,043 patients, with a median age

of 83 years (first quartile Q1: 77; third quartile Q3: 88) 52.9% were female. There were 1,062 patients with a documented CMR and 1,981 patients who received usual care. The median number of medicines on admission was slightly higher in the CMR group (Md = 8; Q1: 5; Q3: 11) compared to the usual care group (Md = 7; Q1: 5; Q3: 10); mostly driven by a higher percentage of patients with more than 10 medicines in the CMR group. On discharge there was no difference in the median number of medicines between the groups, where the median for CMR and usual care was equal (Md = 9; Q1: 6; Q3: 12).

Table 3.1 Characteristics of the study population

Population characteristics		Usual care (N = 1,981)	CMR (N= 1,062)
Age, n (%) (total n = 2,335)	70-74	258 (15.29%)	86 (13.27%)
	75-79	339 (20.09%)	153 (23.61%)
	80-84	412 (24.42%)	119 (18.36%)
	85-89	356 (21.10%)	144 (22.22%)
	≥ 90	322 (19.09%)	146 (22.53%)
Gender, n (%) (total n = 3,034)	Male	950 (48.08%)	479 (45.27%)
	Female	1,026 (51.92%)	579 (54.73%)
Medicines	Admission, Md, Q1-Q3	7, 5-10	8, 5-11
	0 medicines, n (%)	106 (5.51%)	21 (1.98%)
	1-5 medicines, n (%)	510 (26.51%)	274 (25.90%)
	6-10 medicines, n (%)	861 (44.75%)	482 (45.56%)
	> 10 medicines, n (%)	447 (23.23%)	281 (26.56%)
	Discharge	9, 6-12	9, 6-12
	0 medicines, n (%)	110 (5.55%)	19 (1.79%)
	1-5 medicines, n (%)	375 (18.93%)	208 (19.59%)
	6-10 medicines, n (%)	821 (41.44%)	470 (44.26%)
	> 10 medicines, n (%)	675 (34.07%)	365 (34.37%)

	Started	2, 0-4	2, 1-4
	Held	0, 0-0	0, 0-0
	Stopped	0, 0-1	1, 0-2

CMR, comprehensive medication review; Md – median; Q1 – first Q3 and third quartile.

3.3.2 Analysis 2: Changes in prescribing patterns

The second part of the analysis explored the impact of CMR compared to usual care on prescribing patterns. Three independent t-tests were used (tables 3.3, 3.5, 3.7) to establish whether the difference in the mean number of medicines deprescribed, held and started between CMR and usual care was statistically significant.

3.3.2.1 Medicines deprescribed (stopped)

On average, the CMR group had more medicines deprescribed ($\bar{x}$ = 1.44, SE = 0.06) compared to the usual care group ($\bar{x}$ = 0.97, SE = 0.04). See table 3.2.

Table 3.2 Mean number of medicines deprescribed in the CMR and usual care groups

Intervention	N	Mean	Standard deviation	Standard error
CMR	1,048	1.44	1.78	0.06
Usual care	1,882	0.97	1.58	0.04

Table 3.3 contains the t-test statistics. Prior to determining significance, the variances in the CMR and usual care groups were compared to see whether there was any difference, by applying the Levene's test.

Given that results of a Levene's test are significant at p ≤ 0.0125, we have confidence to assume that the variances are significantly different and that the assumption of homogeneity has been violated – in other words, we can assume that the variances are not equal, so I considered test statistics in the row labelled 'Equal variances not assumed'.

On average, a greater number of medicines deprescribed was reported for the CMR group ($\bar{x}$ = 1.44, SE = 0.06) than in the usual care group ($\bar{x}$ = 0.97, SE = 0.04). The difference was statistically significant with a $t(1,957) = 7.09$, $p \leq 0.0125$, $r = 0.03$. This means that we can reject the null hypothesis (hypothesis Ia) that there was no difference between the two groups in the number of deprescribed medicines.

Table 3.3 Independent samples t-test comparing the mean number of medicines deprescribed between CMR and usual care

	Levene's test		t-test for equality of means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95%CI	
								Lower	Upper
Equal variances	33.59	0.00	7.33	2,928	0.00	0.47	0.06	0.34	0.59
Not equal variances			**7.09**	**1,957**	**0.00**	**0.47**	**0.07**	**0.34**	**0.60**

t, t-value; df, degrees of freedom; Sig. significance (p-value); Std. Standard.

3.3.2.2 Medicines held

CMR also resulted in more medicines being held ($\bar{x}$ = 0.21, SE = 0.02) compared to usual care ($\bar{x}$= 0.14, 0.01), as per the table 3.4.

Table 3.4 Mean number of medicines held in the CMR and usual care groups

Intervention	N	Mean	Standard deviation	Standard error
CMR	1,062	0.21	0.70	0.02
Usual care	1,981	0.14	0.57	0.01

The results from the independent samples t-test (table 3.5) showed that the number of medicines held for CMR was significantly higher than the number of medications held following usual care, with a $t(1,832) = 2.85$, $p \leq 0.0125$ and effect size of $r = 0.004$. The null hypothesis (hypothesis Ib) that there was no difference between the two groups in the number of deprescribed medicines was rejected. The results of the Levene's test were significant at $p \leq 0.0125$, which is why equal variances was not assumed.

Table 3.5 Independent samples t-test comparing the mean number of medicines held between CMR and usual care

	Levene's test		t-test for equality of means						
	F	Sig.	t	Df	Sig. (2-tailed)	Mean difference	Std. error difference	95%CI	
								Lower	Upper
Equal variances	29.53	0.00	3.02	3,041	0.00	0.07	0.02	0.02	0.12
Not equal variance			**2.85**	**1,832**	**0.00**	**0.07**	**0.02**	**0.02**	**0.12**

CI, confidence interval; t, t-value; df, degrees of freedom; Sig. significance (p-value); Std. Standard

3.3.2.3 Medicines started

The average number of medicines started was higher in the CMR group ($\bar{x}$ = 2.68, SE = 0.07) compared to the average number of medicines started in the usual care group ($\bar{x}$ = 2.36, SE = 0.05), as per the table 3.6.

Table 3.6 Mean number of medicines started in the CMR and usual care groups

Intervention	N	Mean	Standard deviation	Standard error
CMR	1,062	2.68	2.42	0.07
Usual care	1,981	2.36	2.41	0.05

To test whether the difference between the groups was significant, an independent samples t-test was conducted (table 3.7). The results showed that the number of medicines started in the CMR group was significantly higher than the number of medications started in the usual care group, with a t(3,041) = 3.51, p ≤ 0.0125 and effect size of r = 0.004. The null hypothesis (hypothesis Ic) that there was no difference between the two groups in the number of started medicines was rejected. The results of the Levene's test were not significant at p = 0.196, therefore we can assume that the variances are roughly equal.

Table 3.7 Independent samples t-test comparing the mean number of medicines started between CMR and usual care

	Levene's test		**t-test for equality of means**						
	F	**Sig.**	**t**	**Df**	**Sig. (2-tailed)**	**Mean difference**	**Std. error difference**	**95%CI**	
								Lower	**Upper**
Equal variances	**1.67**	**0.196**	**3.51**	**3,041**	**0.00**	**0.32**	**0.09**	**0.14**	**0.50**
Not equal variance			3.50	2,161	0.00	0.32	0.09	0.14	0.50

CI, confidence interval; t, t-value; df, degrees of freedom; Sig. significance (p-value); Std. Standard

3.3.2.4 Summary of second analysis

CMR was associated with an increase in number of medicines deprescribed (CMR ($\bar{x}$ = 1.44, SE = 0.06) vs usual care ($\bar{x}$ = 0.97, SE = 0.04) ($p \leq 0.0125$)); number of medicines held (CMR ($\bar{x}$ = 0.21, SE = 0.02), vs usual care ($\bar{x}$ = 0.14, SE = 0.01) ($p \leq 0.0125$)); and number of medicines started (CMR ($\bar{x}$ = 2.68, SE = 0.07) vs usual care group ($\bar{x}$ = 2.36, SE = 0.05) ($p \leq 0.0125$)). Therefore, CMR was statistically significantly associated with more changes in prescribing patterns, both in terms of starting and stopping medicines.

3.3.3 Analysis 3: Cost of medicines

The third part of the analyses used independent samples t-tests to compare the costs of medicines between the CMR and usual care groups.

3.3.3.1 Characteristics of costs

Before analysing the cost data, it is important to acknowledge the limitations of the ReMAC study in this aspect. The study was not designed as a cost analysis and as such, much data on the type of medicines deprescribed or started are missing. Without that data the costs for these medicines could not be obtained. Table 3.8 presents the analysis of cost data when only people who have at least one medicine deprescribed are analysed for cost of deprescribed medicines, and similarly when only people with at least one medicine started have the cost of started medicines analysed.

In the CMR group, 481 out of 636 (75.63%) patients with at least one medicine deprescribed had full cost data available. For the started medicines, the percentage was lower, with only 271 out of 859 patients (31.55%) with at least one medicine started having the full cost data available. The average cost-saving from deprescribed medicines was -£17.01 and the average cost of started medicines was £42.84 per patient.

In the usual care group, the recording for deprescribed medicines was high, with the full cost data available for 552 out of 556 (99.28%) patients with at least one deprescribed medicine. There was a large amount of missing data for the started medicines; the full data on cost were only available for 29 of 887 (3.27%) patients

with at least one started medicine. The average cost-saving from deprescribed medicines was -£16.90 and the average cost of started medicines was £25.75 per patient.

Table 3.8 Analysis excluding people with either no deprescribed or no started medicines

	Usual care (N = 1,981)	CMR (N = 1,062)
Number of patients that had medicines:		
Deprescribed medicines (% of all patients)	556 (28.07%)	636 (59.89%)
Started medicines (% of all patients)	887 (44.78%)	859 (80.89%)
Number of patients with available cost data for:		
Deprescribed medicines (% of all people with at least one deprescribed medicine)	552 (99.28%)	481 (75.63%)
Started medicines (% of all people with at least one started medicine)	29 (3.27%)	271 (31.55%)
Average cost per patient for:		
Deprescribed medicines	-£16.90	-£17.01
Started medicines	£25.75	£42.84

Table 3.9 presents the analysis of cost data for all patients with full cost data, not just the ones with at least one medicine deprescribed or at least one medicine started. This group is larger than the one described in table 3.8, as it includes the £0 cost for patients that did not have any medicines deprescribed or started. This is important, because the CMR compared to usual care increases the number of both deprescribed and started medicines. Therefore, if we do not take account of people who have £0 cost, the data are not fully represented.

In the CMR group, out of 1,062 patients, 870 (81.92%) had full data available on the costs of deprescribed medicines. Recording of start data was again poorer with 474

out of 1,062 (44.63%) patients having full cost data for started medicines. The average cost-saving from deprescribed medicines in the CMR group was -£9.40 and the average cost of started medicines was £24.49 per patient.

In the usual care group, the full cost data were available for 1,896 of 1,981 (95.71%) patients. Full cost data for the started medicines were available for 702 of 1,981 (35.44%) patients. The average cost-saving from deprescribed medicines was -£6.60 and the average cost of started medicines was £5.21 per patient.

Table 3.9 Analysis including people with either no deprescribed or no started medicines

	Usual care (N = 1,981)	**CMR (N = 1,062)**
Number of patients with available cost data (INCLUDING patients that did not have any medicines deprescribed or any medicines started)		
Deprescribed medicines (% of all patients)	1,896 (95.71%)	870 (81.92%)
Started medicines (% of all patients)	702 (35.44%)	474 (44.63%)
Average cost per patient		
Deprescribed medicines	£6.89	£9.67
Started medicines	£5.21	£24.49

3.3.3.2 Data availability for comparison

The available data only allowed comparison of the cost of deprescribed medicines and not the started medicines between the CMR and usual care groups. Overall, 91.02% of full cost data were available for deprescribed medicines for CMR and usual care combined. For the started medicines, full cost data were available for 38.26% of the patients for both groups combined.

There are three reasons why I only conducted a statistical test to compare the cost of deprescribed medicines and not the cost of started medicines. First, the percentage of missing cost data for start medicines is high, with 61.74% missing. Secondly, the data are missing unevenly, where in the CMR group 44.63% of start cost data are available and in the usual care group even less (35.44%). Finally, even

if we would like to proceed with the analysis despite all the missing data, there is an influential bias in the data that cannot be addressed. The 35.44% of full start cost data available include both people who had medicines started and patients who had no medicines started where the cost is £0. Out of these patients, full cost data for patients who had at least one medicine started were available for only 29 patients, that is 3.27% of all usual care group patients with at least one medicine started. If we compare that to the CMR group, the number of patients with full start cost data available was 271 (31.55% of all people with at least one started medicine). That is almost 10 times as many patients, which indicates that the cost of CMR would be estimated much higher than the cost of usual care, because of the sample size. Adding cost for patients who did not have medicines started would not change that, because it is only lowering the average cost for both groups, but not so much the cost difference, due to sampling size bias. The decision was made that the bias was too large to conduct any meaningful statistical analysis for the cost of started medicines. Therefore, comparison of mean cost per patient between CMR and usual care was conducted for deprescribed medicines.

3.3.3.3 Summary: cost of deprescribed medicines

The analysis of the cost-savings coming from deprescribing medicines in the CMR and usual care groups was based on data from 2,766 individuals. The average cost-saving per patient from deprescribed medicines is higher in the CMR group ($\bar{x}$ = -£9.67, SE = 0.46) compared to the savings coming from deprescribed medicines in the usual care group ($\bar{x}$ = -£6.89, SE = 0.27), as per the table 3.10.

Table 3.10 Mean reduction in costs per patient resulting from deprescribing medicines (CMR vs usual care)

Intervention	N	Mean (£)	Standard deviation	Standard error
CMR	870	-9.67	13.42	0.46
Usual care	1,896	-6.89	11.42	0.27

The results from the independent samples t-test (table 3.11) showed that the cost-savings per patient from deprescribing medicines were significantly higher in the CMR group than in the usual care group, with $t(1,494) = -5.27$, $p \leq 0.0125$ and effect size of $r = 0.015$. The null hypothesis (hypothesis II) that there was no difference between the two groups in the cost of deprescribed medicines per patient was rejected. The results of the Levene's test were significant at $p \leq 0.0125$, which is why equal variances was not assumed.

Table 3.11 Independent samples t-test comparing mean cost-savings per patient resulting from deprescribing medicines (CMR vs usual care)

	Levene's test		t-test for equality of means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95%CI	
								Lower	Upper
Equal variances	17.93	0.00	-5.55	2,764	0.00	-2.78	0.50	-3.77	-1.80
Not equal variances			**-5.27**	**1,494**	**0.00**	**-2.78**	**0.53**	**-3.82**	**-1.75**

CI, confidence interval; t, t-value; df, degrees of freedom; Sig., significance (p-value); Std., standard

3.3.4 Analysis 4: Impact of CMR, age and gender on the difference in number of medicines

This analysis looked at the effect of CMR on the difference between number of medicines on admission and compared with discharge. In order to test which patients' characteristics had an impact on the number of medicines, a three-way (2x2x5) ANOVA was conducted to test whether a three-way interaction effect exists between CMR, age and gender in explaining the difference in number of medicines.

Before introducing the different tests, the Levene's test was conducted to test whether there is any difference between variances. The results of the Levene's test were not significant; therefore, we can assume that the variances are roughly equal (table 3.12).

Table 3.12 Levene's test of equality of error variances for difference between medicines on admission and medicines on discharge [a,b]

	Levene statistic	df1	df2	Sig.
Based on mean	1.041	19	2,306	0.409
Based on median	1.109	19	2,306	0.334
Based on median and with adjusted df	1.109	19	2,207	0.334
Based on trimmed mean	1.083	19	2,306	0.361

df, degrees of freedom; sig., significance (p-value).
Tests the null hypothesis that the error variance of the dependent variable is equal across groups.
a. Dependent variable: difference between medicines on admission and medicines on discharge
b. Design: Intercept + CMR + age bands + Gender + CMR * age bands + CMR * Gender + age bands * Gender + CMR * age bands * Gender

3.3.4.1 Main effect

The analysis looked at three main effects: CMR, age and gender (hypotheses III-V), the results are presented in table 3.13).

The analysis revealed that there was a significant main effect of CMR on the difference in number of medicines ($F(1, 2{,}306) = 40.51$, $p < 0.05$), where patients

who received CMR had fewer additional medications at discharge (CMR +0.96 medicines vs usual care +1.32 medicines at discharge).

There was a no significant main effect of age (F (4, 2,306) = 1.93, p = 0.103) or gender (F (1, 2,306) = 0.03, p = 0.853) on the difference in number of medicines.

3.3.4.2 Two-way interactions

The analysis of two-way interaction (hypotheses VI-VIII) revealed there was a significant interaction effect between receiving a CMR intervention and age on the difference in number of medicines (F (4, 2,306) = 2.66, p < 0.05) (table 3.13). This suggests that different age groups were affected differently by CMR intervention. The interaction effect was also significant between age and gender regardless of receiving CMR or usual care (F (4, 2,306) =3.34, p < 0.05). This suggests that male and female genders are affected differently by age.

Further analysis revealed that in all but one age group CMR resulted in fewer additional medicines at discharge compared to usual care. The only exception was the male age 80-84-year-old group, in which CMR resulted in an additional 1.43 medicines being prescribed at discharge compared to 1.16 for usual care. For the male age 85-89-year-old group, even though CMR resulted in fewer additional medicines at discharge (CMR +0.82 medicines vs usual care +0.95 medicines), the difference was much lower compared to the rest of the age groups. The effect of age for two age groups – 80-84-year-olds and 85-89-year-olds – was visible for males (figure 3.2); in females this change was not visible (figure 3.3).

There was a non-significant interaction effect between receiving CMR and gender of patient on the difference in number of medicines (F (1, 2,306) = 0.34, p = 0.561).

3.3.4.3 Three-way interactions

Finally, a three-way (2x2x5) ANOVA showed a borderline statistically significant interaction effect between all three variables: CMR, age and gender *(F*(4, 2,306) = 2.33, *p* = 0.054) (hypothesis IX). The results of the analysis are presented in table 3.13).

For the main effects of CMR and gender as well as gender x age interaction, the model degrees of freedom were 1 (df_M = 1). For the main effects of age, CMR x age interaction, age x gender interaction and CMR x age x gender interaction the degrees of freedom were 4 (df_M = 4). For all the effects, the degrees of freedom for the residuals were 2,306 (df_R = 2 306).

Table 3.13 Three-way ANOVA tests of between-subjects effects (CMR, age, gender) on dependent variable: difference in number of medicines

	Type III sum of squares	df	Mean square	F	Sig.
Corrected model	521.14[a]	19	27.43	4.10	0.00
Intercept	934.67	1	934.67	139.61	0.00
CMR	271.17	1	271.20	40.51	0.00
Age	51.65	4	12.91	1.93	0.10
Gender	0.23	1	0.23	0.03	0.85
CMR * age	71.24	4	17.81	2.66	0.03
CMR * gender	2.26	1	2.26	0.34	0.56
Age * gender	89.54	4	22.38	3.34	0.01
CMR * age * gender	62.48	4	15.62	2.33	0.05
Error	15,438.18	2,306	6.70	-	-
Total	17,919.00	2,326	-	-	-
Corrected total	15,959.32	2,325	-	-	-

a. R Squared = 0.033 (adjusted R squared = 0.025)
df, degrees of freedom; sig., significance (p-value).

Figure 3.2 Effects of three-way interaction between age, gender and CMR on the difference between medicines on discharge and medicines on admission (males)

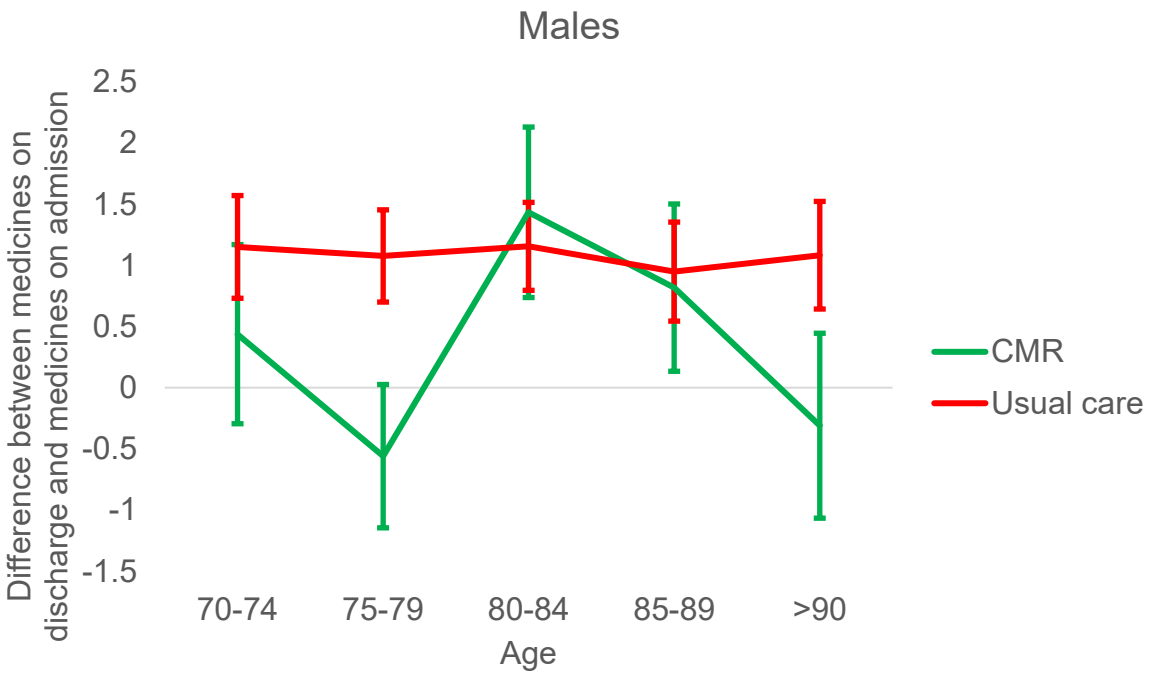
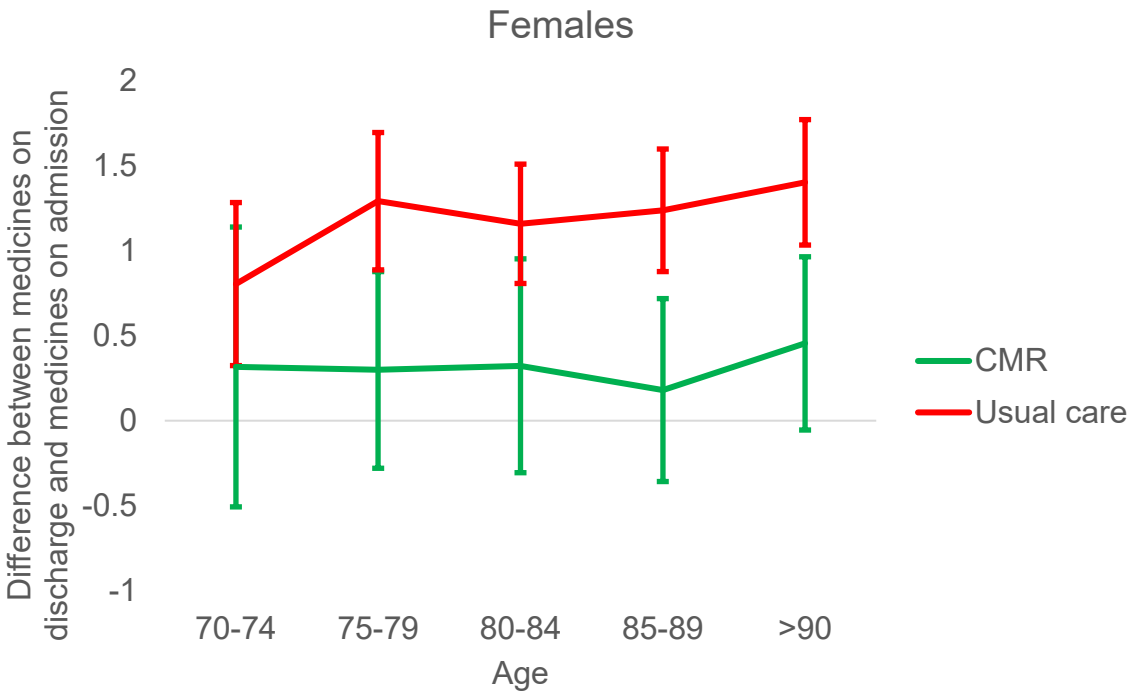


Figure 3.3 Effects of three-way interaction between age, gender and CMR on the difference between medicines on discharge and medicines on admission (females)



3.4 Discussion

3.4.1 Contribution to the field

The study from this chapter addresses the gap in the literature about understanding the application of CMR for inpatient care and how the patterns of prescribing and costs are affected. The study also explored the interaction effect of CMR, gender and age on number of medicines.

Patterns of prescribing

The study informs the literature by providing new information on how receiving CMR impacts the change in the number of medicines. New evidence is available on the effect of CMR compared with usual care in terms of reducing the overall polypharmacy burden. The main outcome measure was the difference between the number of medicines on discharge and on admission. A few studies looked at the effects of CMR on the overall number of medicines patients receive. However, to my best knowledge, this is the only study that looks at patterns of prescribing and compares the number of deprescribed, held and started medicines between CMR and usual care groups.

As described in the background section, the current literature has largely focused on measuring the effectiveness of CMR in reducing specific health outcomes such as mortality, ADE, readmissions and ED visits (Christensen & Lundh, 2013, 2016; Graabaek & Kjeldsen, 2013; Hill-Taylor *et al*., 2016; Hohl *et al*., 2015). However, due to short follow-up in the studies, many treatment effects may have been overlooked as the adverse effect of potentially inappropriate prescribing may take longer to develop. Reduction in overall polypharmacy burden and difference in prescribing patterns for patients receiving CMR can serve as potential intermediate outcome measures for effectiveness of CMR.

The data from this study suggest that compared to usual care, CMR leads to a lower difference between the number of medicines on discharge and medicines on admission. The medicines that are deprescribed are not only PIP medicines, but also other medicines that are no longer necessary for patients. Looking at the reduction in the number of all medicines prescribed for CMR patients compared with usual care

is important. Firstly, because the standard PIPs list (such as STOPP/START or Beers criteria) may not capture all the medicines which are potentially harmful or no longer needed. Looking beyond just the PIP list can show the appropriateness of medicines judged by physicians on a case-by-case basis. Secondly, looking at just the reduction in PIP rates for costing studies of CMR can underestimate the real impact of CMR on reducing the cost of deprescribed medicines.

The results from this chapter showed that the number of medicines per patient increased in both CMR (+0.96 medicines) and usual care groups (+1.32 medicines) from admission to discharge. Four studies included in the systematic literature reviews examined similar outcome measures (Frankenthal *et al*., 2014; García-Gollarte *et al*., 2014; O'Dell & Kucukarslan, 2005), as did a subsequent update of the Frankenthal *et al*. study (Frankenthal *et al*., 2017).

Three studies that compared CMR with usual care in terms of reduction/increase in number of medicines following the intervention (Frankenthal *et al*., 2017, 2014; García-Gollarte *et al*., 2014) all reported a decrease in the number of medicines in the CMR group. In the (García-Gollarte *et al*., 2014) study, the mean number of medicines per patient decreased in both the CMR (-4.61 medicines) and usual care groups (-3.41 medicines). In the (Frankenthal *et al*., 2014) study the average number of medicines prescribed after 12 months was significantly lower in the CMR group (-1.5 medications) compared to the usual care group ($P < 0.001$). The effects of CMR were preserved in a subsequent follow-up study after 24 months, where CMR still resulted in reduction of prescriptions (-1.5 medicines) and the usual care group resulted in an increase (+0.1 medicines); the difference was statistically significant ($p = .03$).

The fact that in the current literature CMR resulted in a decrease in the number of medicines after intervention and in ReMAC there was an increase in the number of medications after intervention could be attributed to the different severity of the disease for the two populations. In ReMAC most of the patients were frail elderly admitted to an acute ward; many of the patients had life-threatening conditions. In Frankenthal *et al*., 2017, 2014 and García-Gollarte *et al*., 2014 the patients were also frail elderly, however the CMR occurred in a long-term care facility and the patients were in a stable condition.

What is important is the fact that the difference between the two groups (CMR and usual care) reported in the literature was consistent with the study from this chapter. In all the studies the CMR group was associated with a lower number of medicines at discharge than the usual care group.

Another study (O'Dell & Kucukarslan, 2005) looked at the average number of medicines prescribed at discharge for both groups, but it did not report a baseline number of medicines, so it was not possible to determine the impact on increasing/decreasing the number of medicines. It reported the average number of medicines at discharge as $\bar{x}$ = 8.4; SD =2.8 for the CMR and $\bar{x}$ = 8.1; SD = 2.4 for usual care; the difference was not statistically significant (p = 0.39).

The studies described above did not look at patterns of how this change occurred. The study in this chapter provides new data that CMR resulted in both a statistically significant increase in the number of medicines deprescribed and a statistically significant increase in the number of medicines started. The results show that the change in the number of medicines at discharge between CMR and usual care is mostly driven by the number of medicines deprescribed, suggesting that CMR reduces the polypharmacy burden for hospitalised patients.

Cost of medicines

The results from this chapter align with the findings from the literature, where the average saving per patient from deprescribed medicines was significantly larger in the CMR group ($\bar{x}$ = -£9.67, SE = 0.46) compared to the usual care group ($\bar{x}$ = -£6.89, SE = 0.27); ($p \leq 0.0125$). Unfortunately, due to limitations of the data it was not possible to conduct meaningful analysis of the difference between the cost of started medicines in the two groups. The study from my PhD is so far the biggest study conducted in which full cost data were collected for 2,766 individuals. The previous largest study (Gallagher *et al*., 2011) looked at 382 individuals and did not collect the cost data but only reported the researcher's opinion about the appropriateness of costs. The study shows that the savings are statistically significant, but the savings might be overestimated in the much smaller studies curried out so far.

A second added value of the study from this chapter is that the study was not an effectiveness trial of the intervention; the study reflected the cost under 'real-world' clinical conditions and not in a controlled trial environment. This allows for much more accurate capturing of costs in current clinical care.

There were three studies included in the systematic literature reviews (presented in chapter 1 and 2) that looked at cost of medicines as an outcome measure.

In the (Frankenthal *et al*., 2014) study that compared 183 patients receiving CMR with 176 patients in the usual care group, the average savings were -£23.49[3] per month per patient larger in the CMR group compared with the usual care group, with the difference being statistically significant. The savings reported in my study (mean cost-savings of -£2.78 (95%CI £3.82; £1.75) per month per patient) were lower compared with Frankenthal *et al*. study, but both results were statistically significant. In the follow-up to the study (Frankenthal *et al*., 2017) over 24 months the same results were observed.

The second study (Gallagher *et al*., 2011) compared CMR (n = 190) with usual care (n = 192), however the study did not provide an estimate for the average cost of medicines. Instead, it looked at the appropriateness of cost of medicines in two groups as measured by the Medication Appropriateness Index (MAI). The percentage of medicines researchers marked as 'medicine not being the least expensive option available for the same benefit' by the end of the study was statistically significantly lower in the CMR group (28% of medicines) than in the usual care group (34% of medicines) ($p < 0.001$).

The third study (Fertleman *et al*., 2005) was a pre- and post- intervention study, in which hospitalised patients pre-intervention received usual care and then switched to CMR. The study was small and included 62 patients with notes identified for 50 patients. The mean saving per patient per month was larger in the CMR group compared with usual care group, which on average was -£6.92 per month per person. The mean savings for CMR compared to usual care in my study were lower.

[3] Originally reported in USD, a at a price base of 2014. The cost was converted using the exchange rate from January 2018; 1 USD = 0.7364 GBP and adjusted for inflation.

Interaction effect of CMR, gender and age on number of medicines

The three-way (2x2x5) ANOVA showed a borderline statistically significant interaction effect between CMR, age and gender on the difference in the number of medicines. Subsequent independent analysis of all three variables revealed that only CMR had a significant main effect on the difference in the number of medicines ($F(1, 2{,}306) = 40.51$, $p < 0.05$) with patients who received CMR having fewer additional medications at discharge than usual care patients (CMR +0.96 medicines vs usual care +1.32 medicines at discharge).

There was also a statistically significant interaction effect between age and gender regardless of having CMR or usual care ($F(4, 2{,}306) = 3.34$, $p < 0.05$). For females age did not impact on the difference between medicines on admission and medicines on discharge; for males, however, there was a noticeable impact, especially for the two age groups 80-84-year-olds and 85-89-year-olds. The increase in the number of medicines for these two age groups relates to the fact that the patients had more medicines started compared to other age groups or compared to females of the same age groups. To my knowledge this has not been observed in any other study investigating the CMR intervention. This finding could be just an anomaly in the data; however, it could also suggest that CMR intervention is more effective for females (80-89-years old). However, this would require further confirmatory study which was outside the scope of this PhD.

3.4.2 Contribution to thesis and implication for further research

This study directly addresses the gap in the literature set out in the introduction about how CMR is applied in inpatient hospital settings and how CMR impacts on prescribing patterns and costs. Understanding the impact of CMR on the number of medicines patients have at discharge is instrumental in structuring the cost-effectiveness model, but also suggests parameters that might be useful to include in the model.

Both CMR and usual care resulted in an increased number of medicines patients received at discharge, although the increase after CMR was smaller. This is because the number of medicines deprescribed in the CMR group was larger than for the

usual care group. Even though CMR also increased the number of medicines started, CMR was still more effective in reducing overall polypharmacy burden, because patients receiving CMR were discharged with fewer additional medicines.

Understanding the patterns of prescribing (if the number of medicines deprescribed or number of medicines started results in change of overall polypharmacy burden) is essential to understanding the purpose and end results of the CMR.

The data from this chapter were used to populate a long-term cost-effectiveness model of CMR vs usual care presented in chapter 6. The information on costing of potentially inappropriate prescribing and the cost of alternative medicines prescribed in place of these PIPs was directly sourced from this chapter. The prescribing patterns and the overall costing of the medicines informed the decision tree and Markov models used in chapter 6.

As mentioned in section 3.3.3.2, the data from the ReMAC initiative were not complete in terms of costs of all the medicines deprescribed and started. Only around 9% of data were missing for the deprescribed medicines, but more than 62% of data were missing for the number of medicines started. Based on this the information on the difference in cost of deprescribed medicines for CMR vs usual care group is more reliable than the information about difference in cost of started medicines. Future research can focus on estimating the difference in cost of started medicines between CMR and usual care groups. Understanding the difference between started and deprescribed medicines in both CMR and usual care can help understand the difference in terms of direct cost of medicines prescribed for both groups. However, the cost of medicines is not the only cost that influences the decision on the economic impact of CMR. To understand the impact of CMR on other long-term costs (e.g. hospitalisation cost for treatment of ADE of medicines) and the impact on patient' health, a cost-effectiveness analysis needs to be conducted.

Recommendation for future research based on this chapter is to conduct a cost-effectiveness analysis of CMR intervention that incorporates both short and long-term costs and health benefit for patients. The recommendation has been addressed jointly by chapters 4 and 6. Chapter 4 is a short-term cost-effectiveness

analysis of CMR vs usual care for the general population of hospitalised patients in UK NHS acute care. Chapter 6 is a long-term cost-utility model of CMR vs usual care, using a narrower target population (patients with heart failure) that allows modelling the cost-utility of CMR over longer time horizon.

Another recommendation for future research relates to comparing the effectiveness of CMR based on gender. This chapter showed that for women age did not make a difference to the number of medicines prescribed, whereas for men CMR was less effective for age groups (80-89-years-old) and was a key factor in terms of number of medicines prescribed following a CMR intervention. A study could be conducted with a research hypothesis that CMR is more effective in reducing the polypharmacy burden for females aged 80-89 compared to males in the same age group. This could be an anomaly in the data from the ReMAC study and further confirmatory study would be required to establish the gender difference in effectiveness of CMR. Gender difference was not studied in the cost-effectiveness modelling conducted in further chapters, as there were no readily available data or other evidence that would allow us to measure the effectiveness of CMR based on gender.

3.4.3 Strengths and limitations

The current literature provides information about the incremental change in the number of medicines for patients at admission and the subsequent change in the number of medicines on discharge. The strength of my study is that it is the first study that has looked at the difference in patterns of prescribing and costs (for deprescribed, started and held medicines) as a result of either CMR or usual care for inpatients in a hospital setting. This study has helped us to understand that the main effect of CMR on prescribing patterns is the number of medicines being deprescribed.

The second strength of this study is the sample size which was 3,043 patients across five acute teaching hospitals in London. To my knowledge this is the largest study that looked at the effects of CMR on prescribing and costs for inpatients. In the discussion I compare my study to similar studies from the literature (3.4.1). The biggest one was (García-Gollarte *et al*., 2014)), which included 716 patients. This large sample size of ReMAC study allowed to showcase the difference between

CMR and usual care in prescribing patterns, because in all the t-tests conducted the p-values were very low. The three-way ANOVA also revealed that CMR had a main effect on the difference in the number of medicines, with a very low p-value.

Another strength is that all the assumptions were tested with a rigorous statistical approach. Before proceeding to do statistical analysis, all appropriate assumptions of homogeneity of variances were checked to make sure that the appropriate tests were used.

First limitation of the study is that the ReMAC study (from which the data for the analysis are drawn) was not designed as an experimental trial to compare the effectiveness of CMR vs usual care. The ReMAC study was a quality improvement initiative which aimed to improve the quality and consistency of CMR intervention. Because the study was not designed for evaluation of effectiveness there could potentially be biases associated with the results. There was no randomisation between the CMR and usual care groups, which can result in selection and allocation bias. The study was not a blinded study and was not designed as a cohort study. The two groups represented a real clinical situation in which some patients received the intervention and others did not. Therefore, in some of the cases the pharmacist or physicians caring for patients could have decided that the patients did not require CMR. However, judging by the fact that by the end of the quality improvement study the number of CMRs increased from 4% to 63%, we can assume that most of these patients did require CMR intervention.

Second limitation is the fact that the outcome measure in the ReMAC study only included CMR intervention if it was documented; there could have been more CMRs delivered that were not documented in the DSUM or patients' notes.

Third limitation is that four t-tests were conducted and with each additional t-test the risk of a type I error increases, which is the rejection of a true null hypothesis. This was addressed by doing a Bonferroni correction to counteract the problem of multiple comparisons. With four independent samples t tested, the p-value was 0.0125 (0.05 divided by 4), and even with the lower p value, all the comparisons still proved to be statistically significant.

Forth limitation was that for all the t-tests conducted, the results were statistically significant, but the effect size was low. For the deprescribed medicines the effect size was r = 0.03, for held r = 0.004, for started r = 0.004 and for differences in costs of deprescribed medicines it was r = 0.015. Although all the tests represented a low effect size, one can argue that the clinical effect is significant. Taking as an example deprescribed medicines, the statistically viewed effect size was just r = 0.03, but CMR reduced on average 0.5 more medicines per patient. Knowing that at admission these patients are on a median of eight medicines and by the time they are discharged they leave hospital with nine medicines, lowering the polypharmacy on average by even half a medication might be important. The literature suggests that for patients on three medicines or more with each additional medicine their risk of having a potentially inappropriate prescription increases by 14-15% (Hudhra *et al*., 2016). The literature also suggests that each additional medication increases the risk of readmission with an odds ratio of 1.04 (Basnet *et al*., 2018). The same thing applies for the cost of medicines where the savings from deprescribed medicines is -£2.78 for the CMR group compared with usual care. If we multiply the number of patients at a hospital level, all hospitals in a region, or the whole country, the savings will be large. Therefore, one could argue that the even through the statistically viewed effect size is low, the clinical and economic impact is large and significant.

3.5 Conclusions

The present study assessed the difference in the number of medicines deprescribed, held and started as well as the savings from deprescribed medicines between CMR and usual care groups. CMR was associated with an increase in the number of medicines deprescribed, number of medicines held and number of medicines started. These results suggest that CMR is associated with statistically significantly more changes to the medication, both newly prescribed and stopped. However, further analysis compared the total difference between medicines on discharge and medicines on admission for both groups, to see whether the CMR leads to an increase or decrease of medicines being prescribed compared to the usual care group. Both the CMR and usual care groups increased the number of medicines patients had at discharge, but patients receiving CMR were discharged with fewer

additional medicines. There was a statistically significant main effect of CMR on the difference between the number of medicines on discharge and on admission.

The savings from deprescribing medicines were statistically significantly larger in the CMR group compared with the usual care group, which on average was -£2.78 per month per patient.

A three-way (2x2x5) ANOVA was used to see whether there was an interaction effect between age, receiving CMR and gender. There was a borderline statistically significant interaction effect between all three variables. When variables were tested independently only CMR was associated with the difference between medicines on discharge and medicines on admission. Two-way analysis found an interaction effect between CMR and age, as well as between age and gender of patients.

CHAPTER 4 SHORT-TERM COST-EFFECTIVENESS OF COMPREHENSIVE MEDICATION REVIEW

This chapter presents findings from a short-term cost-effectiveness model of CMR conducted in acute care. The main purpose of this chapter is to answer research question number 3 .

Is CMR a cost-effective intervention for the general population of elderly acutely hospitalised patients, over a short-term (12-month) time horizon, compared with usual care, from the perspective of the UK NHS?

This chapter presents the justification for conducting the analysis of cost-effectiveness of CMR and how this contributes to the PhD as a whole. I present a brief background describing the decision problem and, in the methods section, the PICO (Population, Intervention, Comparator, Outcome) of the analysis and the data sources used in the model are described. I then present the parameters chosen for the model and finally describe the model designed to solve the decision problem. In the results section, the base-case analysis results and results from deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) based on 10,000 second-order Monte Carlo simulations are presented. The discussion explores the contribution of this study to the field in general, the contribution to the PhD, strengths and limitations of this study and what the implications are for further research. I discuss the question of which healthcare professional should conduct CMR and initiate discussion about the target population of patients who would benefit most from CMR (which leads to chapter 5: Target population). The final section presents the conclusions of this chapter.

The model used in this chapter had two set objectives:

1. Explore the cost-effectiveness of CMR delivered in hospital for a general population of elderly patients at risk of inappropriate prescribing from the UK NHS perspective (this is in contrast to chapter 6, which presents long-term cost-effectiveness analysis, but for a narrower group of patients).
2. Establish whether it was worth pursing long-term cost-effectiveness analysis of CMR. The study was an early indication of possible cost-effectiveness of

CMR, which determined the way forward for the whole PhD. The recommendations from this chapter were implemented in chapters 5-6.

4.1 Background

As discussed in chapter 1, the prevalence of problematic polypharmacy is high, is increasing and is leading to several undesirable health consequences. Problematic polypharmacy can cause adverse drug events, drug-drug interactions, low adherence, reduced quality of life and increased treatment cost (Christensen & Lundh, 2016; NICE, 2014). More information is in section 1.1 ‘Polypharmacy and comorbidities’ of chapter 1.

A Cochrane systematic literature review found that by optimising prescribing CMR may reduce emergency department reattendances by 27% (Christensen & Lundh, 2016). However, the cost-effectiveness of CMR in the UK NHS acute care setting is so far unknown.

To address this gap in literature, a cost-effectiveness analysis (CEA) was conducted. CEA is a method used to present the impact of costs and benefit of an intervention to help decision makers with an evaluation of the economic merits. CEA evaluates the effectiveness of CMR compared with usual care to determine the value for money of the intervention.

4.2 Methods

4.2.1 Overview

The design of the study is a cost-effectiveness analysis, where the results are presented as cost per additional benefit generated or the incremental cost-effectiveness ratio (ICER) presented in formula 4.1.

The health benefit was expressed in natural units as the probability of avoiding emergency department reattendance.

The costs included in the analysis were the costs associated with the interventions and the potential savings to the NHS of costs associated with emergency department reattendance.

$$ICER = \frac{\text{Additional cost of CMR compared to usual care (UC)}}{\text{Additional preventable ED reattendance avoided from CMR compared with UC}} \quad (4.1)$$

A decision tree model was developed in Microsoft Excel to assess the cost-effectiveness of CMR. The model was designed through discussions with healthcare professionals (including pharmacists and medical consultants) and based on the best available evidence from literature and routinely collected data.

Chapter 1 described the six systematic literature reviews that explored the clinical effectiveness of CMR in a hospital setting. The data used in the model from this chapter come from the Cochrane systematic literature review (Christensen & Lundh, 2016). The other review (Hill-Taylor *et al*., 2016) which looked at intermediate effectiveness outcomes (reduction of PIP) of CMR was used for modelling conducted as part of chapter 6, where a long-term cost-effectiveness of medication review was explored.

Four other systematic literature reviews were not selected. One review was the previous version of the Cochrane review (Christensen & Lundh, 2013) analysed in this chapter. In two other reviews the inclusion criteria for the intervention were too broad (for example not only medication review, but also medication reconciliation) (Hohl *et al*., 2015; Kaboli *et al*., 2006); in the fourth review no meta-analysis was performed (Graabaek & Kjeldsen, 2013).

As most studies had a short period of follow-up with too much uncertainty regarding the effect of CMR lasting over 12 months, the time horizon for the analysis was limited to 12 months and there was no need to apply discounting to the costs and the effect measures.

4.2.2 Population

NICE suggests conducting CMR for patients with long-term conditions and polypharmacy who are elderly (NICE, 2015a). The prevalence of polypharmacy increases with age. A study conducted in six acute geriatric medicine units across Europe determined the prevalence of polypharmacy and suggested that 39% of patients 65 years or older received one to five medications; 44% received between six and ten medications and 14% received more than ten medications (Gallagher *et al*., 2011).

In my study, the costs and health consequences of CMR were estimated under the assumption that CMR was available to all acutely hospitalised NHS patients aged 65 years or older. Further subgroup analyses were conducted for different age groups in the model to understand the key drivers of cost-effectiveness. The subgroup analyses alter the model parameters to represent values to a specific subgroup of patients. The aim of the subgroup analyses is to increase population health gains by identifying the group of patients for which health gain is bigger than health outcomes from other health technologies (Sculpher, 2008).

The population considered in the Cochrane systematic review (Christensen & Lundh, 2016) that looked at effectiveness of CMR were all hospitalised patients, excluding patients admitted to paediatric departments, outpatients and patients who contacted the emergency department. Four studies measured emergency department reattendances as one of the endpoints. The total number of participants in the four studies was 1,442 patients, with the average age of patients 70.22 years. Table 4.1 below presents the different inclusion criteria for the population in each of the studies (Christensen & Lundh, 2016).

Table 4.1 Included studies – population

Study	Population
(Farris *et al*., 2014)	Hospitalised patients ≥ 18 years acutely admitted to general medicine, family medicine, cardiology or orthopaedics wards with a diagnosis of heart failure, chronic obstructive pulmonary disease, hyperlipidaemia, hypertension, asthma, transient ischemic attack, stroke, myocardial infarction or coronary artery disease or on oral anticoagulation drugs
(Lisby *et al*., 2011)	Hospitalised patients ≥ 65 years acutely admitted to an orthopaedic ward
(Lisby *et al*., 2010)	Hospitalised patients ≥ 70 years admitted to acute internal medicine ward
(Gillespie *et al*., 2009)	Hospitalised patients ≥ 80 years admitted to acute internal medicine wards

4.2.3 Interventions

The intervention used in the analysis was a CMR defined as a 'structured critical examination of all current medication with the objective of reaching an agreement with the patient about treatment, considering the merits and risks of different medications, stopping inappropriate medicines and starting others, optimising their impact, minimising the number of medication-related problems and reducing waste'(Szymanski *et al*., 2016; Ward *et al*., 2019).

The NICE guidelines on medicines optimisation highlight that the appropriate health professional to carry out a CMR should be determined locally (NICE, 2015a). However, all the studies that measured reduction in emergency department reattendances looked at pharmacist-led medication review. Therefore, the base-case analysis assumed the intervention is delivered by a hospital-based pharmacist, whereas in the sensitivity analysis CMR delivered by different healthcare professions was assessed.

4.2.4 Comparator

The comparator for CMR was usual care (UC), that is the routine care received by patients at a given hospital. The countries in which the studies were carried out have similar recommendations to the NHS, where CMR is recommended, but is not compulsory. As indicated in chapter 3, the CMR is rarely implemented and there is room for improvement in terms of quality of CMR, which could potentially be improved if there is evidence for its cost-effectiveness. Chapter 2 describes what constitutes usual care: a medication review done inconstantly, low-quality medication review, ad hoc medication review or noncomprehensive medication review. Other interventions that reduce potentially inappropriate prescribing (PIP) were not included as comparators, as there is no consensus on the standard approach to reducing PIP. All the studies included in the systematic literature review compared CMR against UC.

4.2.5 Outcomes

Clinical effectiveness

All clinical effectiveness aspects from the Cochrane systematic review (Christensen & Lundh, 2016) were considered for inclusion in cost-effectiveness analysis, including mortality, emergency department readmissions, hospital readmissions and the number of reported adverse drug events. In the review, the authors concluded that CMR undertaken in hospital may reduce emergency department reattendances compared to usual care. The difference in terms of hospital readmissions and mortality was not statistically significant. Therefore, the model follows a conservative assumption that within the 12-month follow-up there was no difference in term of quality of life between the two groups. The probability of avoiding emergency department reattendance was used as a primary outcome in the cost-effectiveness analysis.

The four RCTs from the systematic review (Christensen & Lundh, 2016) included data from 1,442 patients. 860 participants were randomised into the CMR group and 582 into the usual care group. During follow-up, ranging from three to 12 months,

there were 126 patients in the CMR group and 118 patients in the usual care group who experienced at least one emergency department reattendance. From the four studies the relative risk favouring CMR was RR = 0.73 (95% CI 0.52; 1.03). The baseline probability of patients 65 years or older reattending emergency department is 0.59 and comes from the national Hospital Episode Statistics (HES) database from 2012 (table 3), which contains data about all admissions, A&E attendances and outpatient appointments at NHS hospitals in England. Providing there was no evidence to suggest otherwise, adherence to medication regime in the model is the same for both the intervention and control group.

The outcome measure in the cost-effectiveness analysis (ED reattendances adverted) was treated as a proxy for health outcome. There is strong evidence that frequent ED users experience higher adverse outcomes like mortality, hospital admission and outpatient visits, which can all influence QALYs (Moe *et al*., 2015).

Costs and resources

The main cost of a pharmacist-led CMR is assumed to be the additional time required for pharmacists to complete a review. Hospital pharmacists on average need 33.6 min (95% CI 31.9 to 35.5) to complete a CMR (Brodersen Lind *et al*., 2016) with an hourly cost of NHS pharmacist time of £45 (Curtis & Burns, 2018). Hence, the average cost of CMR was estimated to be £25.20.

Apart from the cost of CMR, the model incorporates the cost to the NHS of an emergency department (ED) reattendance. Reference costs were used as the source of data for the cost of ED reattendances, with an estimated cost of £160.32 (table 4.2). These are the average unit costs of providing patient care in the NHS in a given financial year (Reference Cost, 2018). Reference cost collection is nationally mandated for all NHS acute, mental health, ambulance and community trusts in England and is the single largest source of financial data from the NHS (HERC Oxford University, 2019b; NHS Improvement, 2018).

Table 4.2 Parameters used for the model

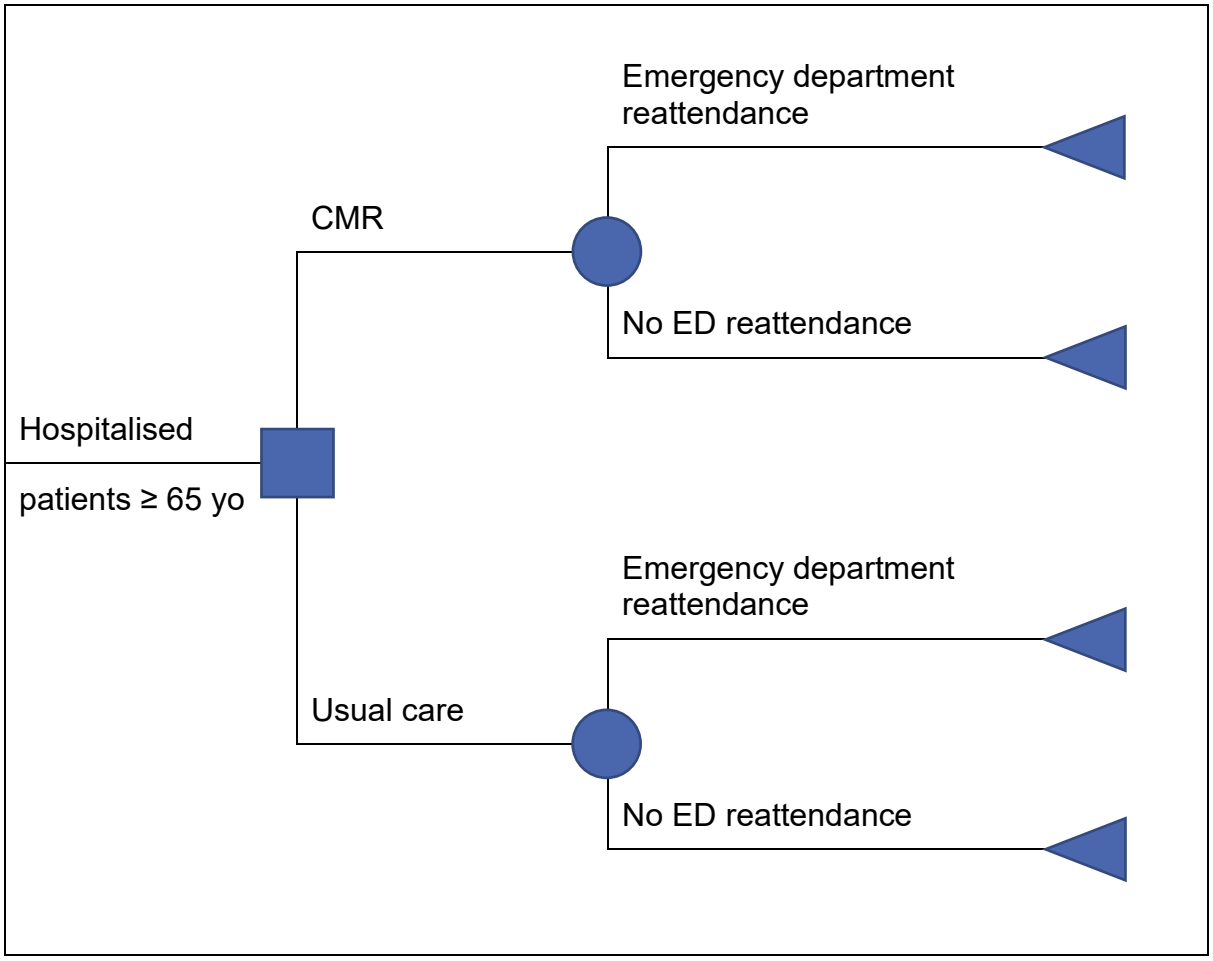
Model parameter	Value of the parameter	Source
Costs		
Pharmacist cost	45 £/h	(Curtis & Burns, 2018)
Cost of CMR	£25.2	(Brodersen Lind *et al*., 2016; Curtis & Burns, 2018)
Cost of ED reattendance	£160.32	(Reference Cost, 2018)
Probabilities		
Probability of ED reattendance (CMR)	0.43	(Christensen & Lundh, 2016; HES, 2012)
Probability of ED reattendance (usual care)	0.59	(HES, 2012)
Relative risk		
Relative reduction in ED reattendances (CMR vs usual care)	0.73 (95% CI 0.52; 1.03)	(Christensen & Lundh, 2016)

ED, emergency department; CMR, comprehensive medication review; CI, confidence interval; reference cost, Reference Cost Collection: National Schedule of Reference Costs - Year 2017 - 18 NHS trusts and NHS foundation trusts; HES 2012, Hospital Episode Statistics 2012.

4.2.6 Model structure

To evaluate the short-term impact of CMR on the general population of elder patients a decision tree model was chosen. The advantage of a decision tree model is its simplicity (see 1.3.2.2 ‘Decision models used for health economics’, for more information on decision tree models). A cost-effectiveness analysis was conducted to capture costs associated with the interventions from a UK NHS perspective with a time horizon of 12 months. For the purpose of the study a de novo decision tree model was developed (figure 4.1). The structure of the decision tree starts with a decision node that indicates choice between CMR and usual care. The choice of the intervention influences the probability of a patient avoiding emergency department reattendance.

Figure 4.1 Decision tree model for CMR and usual care from the UK NHS perspective



ED, emergency department; CMR, comprehensive medication review; yo, years old.

4.2.7 Assumptions for deterministic and probabilistic sensitivity analyses

4.2.7.1 Subgroup analyses

For the subgroup analyses, the values of the baseline probabilities were adjusted to represent the risk of different age groups reattending the emergency department (table 4.3). Upon request, researchers at the Primary Care and Public Health Department of Imperial College London extracted data from the HES dataset on the number of patients and subsequent reattendances to the ED. The data included in the model were based on 4,514,409 ED admissions in the financial year 2011 and 4,777,276 in 2012.

Table 4.3 Number of ED admissions and reattendances within 12 months and the probability of patients reattending ED

Age	Number of ED admissions		Number of ED reattendances within 12 months		Probability of ED reattendance	
	2011	2012	2011	2012	2011	2012
≥ 65 years	4,514,409	4,777,276	2,572,775	2,750,758	0.58	0.59
≥ 70 years	3,155,106	3,337,215	1,879,834	2,011,818	0.60	0.60
≥ 75 years	2,540,452	2,699,641	1,539,559	1,658,098	0.61	0.61
≥ 80 years	1,906,353	2,037,297	1,171,836	1,270,107	0.61	0.62

ED, emergency department; Source: (HES, 2012).

4.2.7.2 Deterministic sensitivity analyses

To account for the uncertainties in the model, a series of one-way deterministic sensitivity analyses was conducted. The deterministic sensitivity analyses were undertaken for different parameter values (e.g. best- and worst-case scenario) but also looked at different structural assumptions (e.g. different healthcare professionals delivering the intervention).

The results of the deterministic sensitivity analysis are presented on tornado diagrams, where on each bar of the diagram one model assumption is altered while the rest remain at the base-case value. Tornado diagrams allow assessment of which parameters have the biggest impact on results when the parameters are changed compared to the base-case analysis (York Health Economics Consortium, 2016f).

Each assumption that is altered is represented with a horizontal bar, which indicates the variation around the central value of ICER (ICER from base-case analysis); (York Health Economics Consortium, 2016f). When changing different parameters, two extreme values were chosen to represent the variation. However, when doing the same for structural assumptions only one value was changed; therefore, one of the ends of the horizontal bar stayed at the central value of base-case ICER, and the

second end of the bar represented the ICER where the structural assumption was made.

The horizontal bars are ordered by their spread, from the largest range to the smallest. The horizontal bars on top of the chart represent the values towards which the model outputs are most sensitive.

Best- and worst-case scenario

The best- and worst-case scenario parameters from the base-case analysis are substituted with extreme values of these parameters. The input values were changed for four of the parameters. They are described below and the values are presented in table 4.4.

1. CMR group: The probability of reattending ED within 12 months of discharge – based on 95% confidence interval of relative risk (RR) of reduction in reattendances by CMR compared to UC.
2. UC group: The probability of reattending ED within 12 months of discharge – based on 95% confidence interval of probability of reattendance.
3. The cost of CMR intervention – based on 95% confidence interval of costs to deliver CMR.
4. The cost of ED reattendance: Although the reference costs index is based on one of the biggest financial datasets in the NHS and is often used in cost-effectiveness analyses, some uncertainties need to be considered. There is the sampling uncertainty, which means that in different financial years the composition of procedures delivered within the emergency department might differ, which can influence the average cost of an ED visit. There could be interventions that are infrequent but which, when they happen, skew the costs. The cost can vary from year to year; even when using the most up-to-date reference costs (which in the case of this PhD is data collected for the financial year 2017 to 2018) they are already outdated by one year. A limitation of the reference cost index publication is that the standard error is not reported in the data, which creates a challenge when it comes to conducting a probabilistic sensitivity analysis. A common approach is to look at the range of variation in the data between all the different organisations that provided the data. To calculate the standard error, we can use the first and

third quartile of emergency medicine unit cost values for different organisations. This can be calculated using the formula (4.2) presented below. However, we must consider that the costs will vary between organisations, within the organisation and even based on the characteristics of a given patient (Snowsill, 2016).

$$SE \approx \frac{Q3 - Q1}{(Z_{0.75} - Z_{0.25})\sqrt{n_t}} \qquad (4.2)$$

SE – standard error

Q3 – third/upper quartile

Q1 – first/lower quartile

n_t – number of NHS organisations on which the unit cost is based

$Z_{0.75}$ – Z Score of 0.75

$Z_{0.25}$ – Z Score of 0.25

(Snowsill, 2016)

Table 4.4 Parameters altered in the best- and worst-case analyses

Probability of ED reattendance (CMR)		
Base-case value	0.43	(Christensen & Lundh, 2016; HES, 2012)
Best-case scenario (based on lower 95% CI)	0.31	(Christensen & Lundh, 2016; HES, 2012)
Worst-case scenario (based on upper 95% CI)	0.61	
Probability of ED reattendance (usual care)		
Base-case value	0.5887	(HES, 2012)
Best-case scenario (based on upper 95% CI)	0.5891	(HES, 2012)
Worst-case scenario (based on lower 95% CI)	0.5881	

Cost of CMR		
Base-case value	£25.2	(Brodersen Lind *et al*., 2016; Curtis & Burns, 2018)
Best-case scenario (based on lower 95% CI)	£23.9	(Brodersen Lind *et al*., 2016; Curtis & Burns, 2018)
Worst-case scenario (based on upper 95% CI)	£26.6	
Cost of ED reattendance		
Base-case value	£160	(Reference Cost, 2018)
Best-case scenario (based on upper quartile)	£216.18	(Reference Cost, 2018)
Best-case scenario (based on lower quartile)	£94.28	

ED, emergency department; CMR, comprehensive medication review; CI, confidence interval; reference cost, Reference Cost Collection: National Schedule of Reference Costs - Year 2017 - 18 NHS trusts and NHS foundation trusts; HES 2012, Hospital Episode Statistics 2012.

Changes in structural assumptions

In chapter 2, I described CMR as a complex intervention, one which can vary between different settings. To account for some of the complexities of CMR, I conducted a sensitivity analysis which modifies some of the key structural assumptions of the model. Below is the description of the altered structural assumptions. The values that were changed are presented in table 4.5.

1. **Healthcare professional delivering the intervention**

   NICE does not specify which healthcare professional should deliver the intervention. In the guide on medicines optimisation (NICE, 2015a), NICE suggests the appropriate healthcare professional should be determined locally. Most studies of CMR are pharmacist-led interventions, which is why in the base-case analysis the assumption is that CMR is delivered by a pharmacist. In this sensitivity analysis, I change that assumption to see how the results change if a doctor or a nurse delivers the intervention. Because the experience of the person delivering CMR may influence its effectiveness, I also analysed different

levels of expertise of healthcare professionals. The analyses were conducted for the following healthcare professionals: hospital-based nurse, pharmacist specialist, pharmacist – advanced, pharmacist – team manager, foundation doctor FY1, foundation doctor FY2, registrar, consultant, associate specialist, consultant: medical (as defined by PSSRU (Curtis & Burns, 2018)).

2. Effectiveness of CMR

The experience and skills of the healthcare professional are not the only things that can influence the effectiveness of CMR. Chapter 2 describes the context in which the intervention is delivered and that it plays a critical role in the effectiveness of CMR. There are several behavioural and systemic factors which can impact positively or negatively on the successful delivery and subsequent effectiveness of CMR. To address this uncertainty, I altered the structural assumption around the effectiveness of CMR, by using data from all available RCTs (Gillespie *et al*., 2009; Hohl *et al*., 2015; Lisby, Bonnerup, *et al*., 2018; Lisby *et al*., 2010), as well as the earlier version of the Cochrane systematic literature review (Christensen & Lundh, 2013).

3. Cost of ED reattendance

The outcome measure in the analysis is the cost of ED reattendance, which on average equals £160 (Reference Cost, 2018). Because the population included in the analysis is broad, patients can be admitted to the ED for different reasons. To represent the variation in the severity and cost of the ED visit by a patient, I modified the structural assumption. In the sensitivity analysis, I looked at costs from national tariff instead of reference cost. The national tariff is based on the reference costs, but because it is used for commissioning it has different prices for different healthcare resource groups (HRG). HRGs group together patient events which require similar levels of resources; for ED reattendance the prices varied between £73 and £338 (National Tariff 2019-20).

Table 4.5 Structural assumption changes of parameters for sensitivity analysis

Model parameter	Value of the parameter	Source
Hourly costs of different healthcare professional work		
Pharmacist cost (base-case value)	45 £/h	(Curtis & Burns, 2018)
Foundation doctor FY1	28 £/h	(Curtis & Burns, 2018)
Foundation doctor FY2	32 £/h	
Hospital-based nurse	37 £/h	
Registrar	43 £/h	
Pharmacist – specialist	55 £/h	
Pharmacist – advanced	65 £/h	
Pharmacist – team manager	77 £/h	
Pharmacist consultant	90 £/h	
Associate specialist	105 £/h	
Consultant: medical	108 £/h	
Effectiveness of CMR		
Base-case value	0.73	(Christensen & Lundh, 2016)
Hohl 2015	0.60	(Hohl *et al*., 2015)
Cochrane 2013	0.64	(Christensen & Lundh, 2013)
Lisby 2011	0.32	(Lisby, Bonnerup, *et al*., 2018)
Lisby 2010	0.98	(Lisby *et al*., 2010)
Gillespie 2009	0.71	(Gillespie *et al*., 2009)

Cost of ED reattendance		
Base-case value	£160	(Reference Cost, 2018)
Tariff HRG VB11Z and type 3 Departments	£73	(National Tariff Payment System, 2019)
Tariff HRG VB09Z	£106	(National Tariff Payment System, 2019)
Tariff HRG VB06Z	£130	(National Tariff Payment System, 2019)
Tariff HRG VB08Z	£155	(National Tariff Payment System, 2019)
Tariff HRG VB07Z	£163	(National Tariff Payment System, 2019)
Tariff HRG VB05Z	£184	(National Tariff Payment System, 2019)
Tariff HRG VB04Z	£227	(National Tariff Payment System, 2019)
Tariff HRG VB03Z	£252	(National Tariff Payment System, 2019)
Tariff HRG VB02Z	£338	(National Tariff Payment System, 2019)
Tariff HRG VB01Z	£338	(National Tariff Payment System, 2019)

FY1, Foundation Year 1; FY2, Foundation Year 2; ED, emergency department; CMR, comprehensive medication review; CI, confidence interval; reference cost, Reference Cost Collection: National Schedule of Reference Costs - Year 2017 - 18 NHS trusts and NHS foundation trusts; HES 2012, Hospital Episode Statistics 2012; HRG, healthcare resource group; National Tariff 2019-20, The 2019/20 National Tariff Payment System.

4.2.7.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to quantify the level of confidence in the results from the model. The input parameters in the model come from systematic literature review of RCTs, from national cost data (Hospital Episode Statistics, PSSRU) and other sources. Although the evidence is some of the best currently available, the parameters that are sourced from the data are not free from uncertainty. In the PSA, rather than being inputted as point values, the parameters

are represented as distributions. Values for the parameters were chosen at random from each of the distributions using second-order Monte Carlo simulation carried out for 10,000 simulations. The model then generated outputs in terms of 10,000 estimates of costs and health outcomes (probability of avoiding ED reattendance) of the intervention. For the relative reduction in ED reattendances the distribution used was LogNormal. Confidence limits for the relative risk are calculated on a log scale, which is why this distribution is the most appropriate (Briggs *et al*., 2006). Because cost data are non-negative and are calculated based on counts of resource use times multiplied by unit costs, the most appropriate distribution was the gamma distribution. Count data are usually represented by Poisson distribution and gamma distribution is conjugate to the Poisson distribution (Briggs *et al*., 2006). The cost values include the cost of ED reattendance. Finally, for probability of ED reattendance for usual care I used the beta distribution as this is the appropriate distribution for binominal data (tables 4.6 and 4.7). The results were presented on a cost-effectiveness acceptability curve, where the proportion of results that favour CMR over UC were plotted in relation to a given cost-effectiveness threshold. The threshold represents the maximum willingness to pay of a decision-maker for an additional health outcome. In this case, the threshold was the value of willingness to pay for the probability of avoiding one additional ED reattendance.

Table 4.6 Parameters used for the model (LogNormal)

Model parameter	Value of the parameter	Distribution	Standard error	Source
Cost of CMR	£25.2 (95% CI 23.93; 26.63)	LogNormal	0.03	(Brodersen Lind *et al.*, 2016; Curtis & Burns, 2018)
Relative reduction in ED reattendances (CMR vs usual care)	0.73 (95% CI 0.52; 1.03)	LogNormal	0.17	(Christensen & Lundh, 2016)

Table 4.7 Parameters used for the model (Gamma and Beta)

Model parameter	Value of the parameter	Distribution	α	β	Source
Cost of ED reattendance	£160.32	Gamma	1,435.43	0.11	(Reference Cost, 2018)
Probability of ED reattendance (usual care)	0.59	Beta	2,384,736	1,666,334	(HES, 2012)

ED, emergency department; CMR, comprehensive medication review; CI, confidence interval; reference cost, Reference Cost Collection: National Schedule of Reference Costs - Year 2017 - 18 NHS trusts and NHS foundation trusts; HES 2012, Hospital Episode Statistics 2012.

4.3 Results

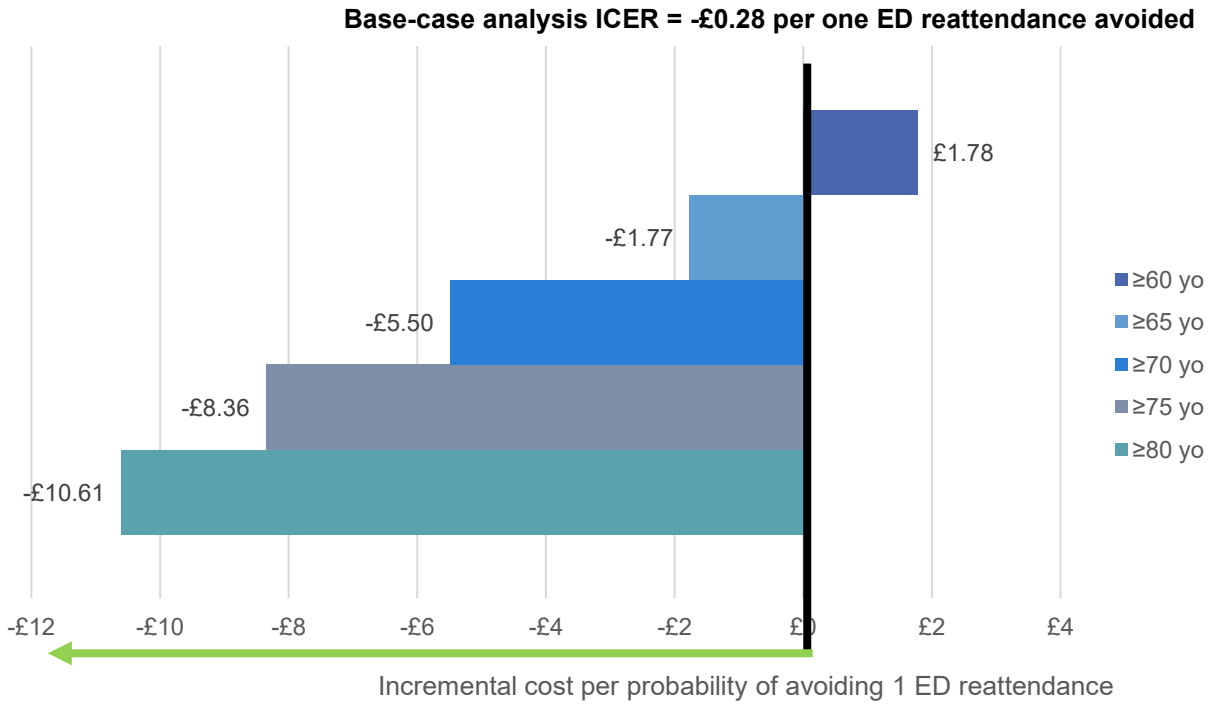
4.3.1 Base-case analysis

In the base-case analysis CMR patients had 0.16 less probability of reattendance to ED while providing savings of £0.28 per patient. The probability of having an ED reattendance for patients in the CMR group was 0.43, compared to 0.59 in the usual care group. From the perspective of the UK NHS, the mean cost per patient in the CMR arm was £94.09, whereas in the UC group it was £94.37. Given that CMR provided more benefits at a lower cost, it dominated the usual care (UC) group. The model estimated that CMR compared with UC saved £1.77 per ED reattendance prevented. The model is based on the best available clinical and cost evidence, however there is uncertainty associated with this evidence. Therefore, a probabilistic and deterministic analysis was carried out to account for the uncertainties in the model.

4.3.2 Subgroup analyses

The higher the age group analysed, the more the incremental cost-effectiveness ratio decreased. This means that CMR becomes a more cost-effective intervention with increasing age of patients. For age group ≥ 60 the ICER was £1.78 per probability of avoiding one ED reattendance; in the age group ≥ 65 the ICER equalled -£1.77 per probability of avoiding one ED reattendance, meaning CMR was a cheaper intervention that provided greater health benefit for patients. The CMR dominated over UC even more as the age of patients increased, with ICER values of -£5.5; -£8.36; -£10.61 per probability of avoiding one ED reattendance for the age groups of ≥70; ≥75; ≥80 respectively. The ICER values for patients in different age groups are represented in figure 4.2.

Figure 4.2 Tornado diagram: subgroup analyses based on age of patients



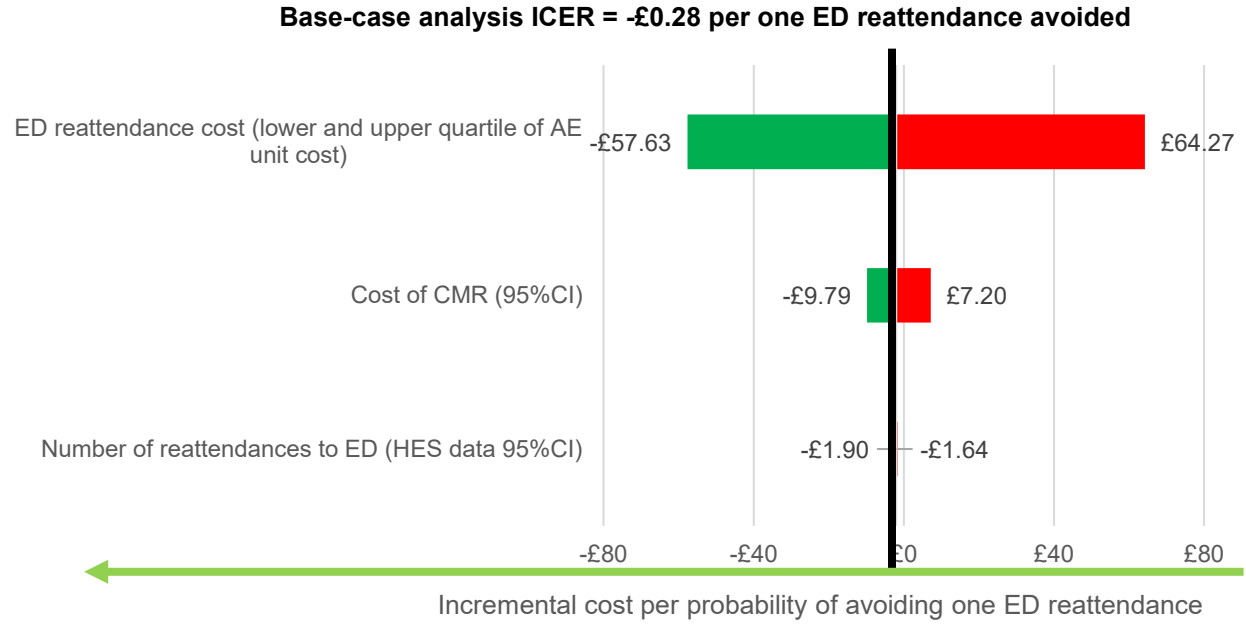
CMR dominates over UC

4.3.3 Deterministic sensitivity analysis

The values of ICER for the cost of ED reattendance ranged from -£57.63 to £64.27 per probability of avoiding one ED reattendance. The ICER was much less sensitive to change in the cost of the CMR intervention, where the range was -£9.79 to £7.20 per probability of avoiding one ED reattendance. The ICER was least sensitive to change when the probability of ED reattendance was altered; the values of ICER were between -£1.90 and -£1.64 per probability of avoiding one ED reattendance (figure 4.3).

On the other hand, the ICER was most sensitive to the uncertainty about the effectiveness of CMR, where values spanned from -£71.13 (where CMR was more effective and less costly) to -£1,587.27 (where CMR was cost incurring and less effective). To avoid confusion, these two values were not presented on the tornado diagram below, since both values of ICER are negative but mean completely opposite things.

Figure 4.3 Tornado diagram: sensitivity analyses best- and worst-case scenario

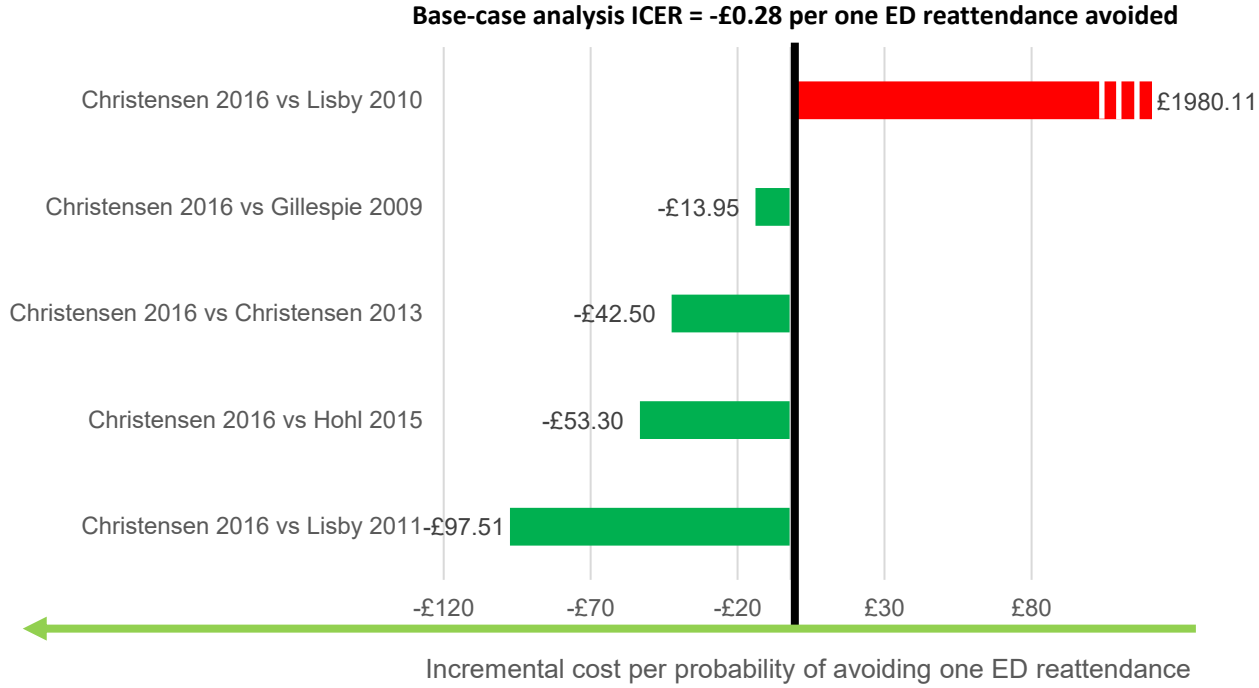


The lower the value of ICER, the more cost-effective CMR becomes.
Green – more cost-effective than base-case; red – less cost-effective than base-case.

Effectiveness of CMR

To explore the sensitivity of ICER towards uncertainty with the effectiveness of CMR in reducing ED reattendances, different structural assumptions were examined. Effectiveness of CMR in reducing ED reattendances was modified in the model to represent different values from different studies which reported this outcome. In all but one study ICER indicated that CMR was still dominating over UC and even to a greater extent, with values of ICER ranging from -£97.51 to -£13.95. Only one study changed the ICER significantly, where the ICER equalled £1,980.11 per probability of avoiding one ED reattendance.

Figure 4.4 Tornado diagram: changes in structural assumptions on effectiveness of CMR in reducing ED reattendances

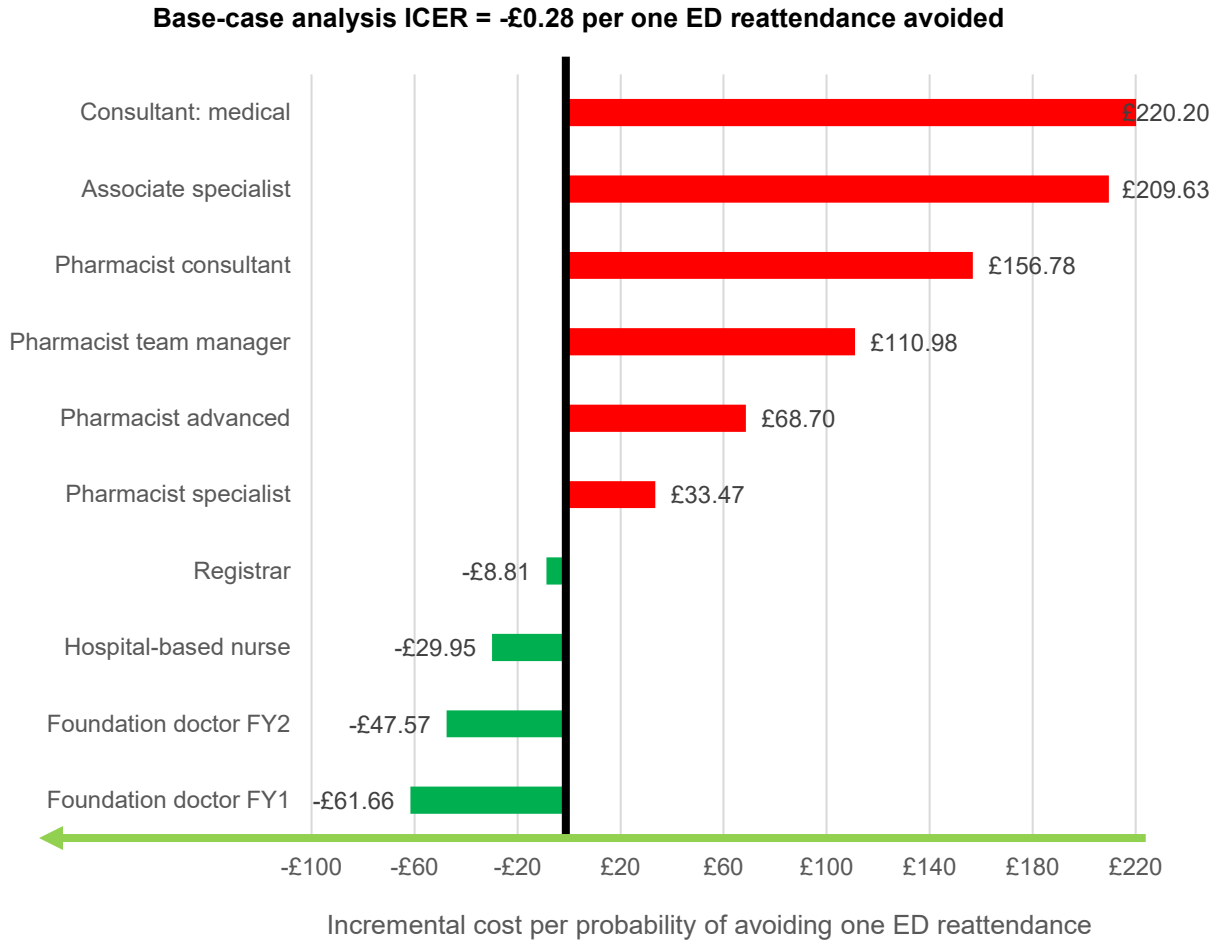


The lower the value of ICER, the more cost-effective CMR becomes.
Green – more cost-effective than base-case; red – less cost-effective than base-case.

Healthcare professional delivering the intervention

In the deterministic sensitivity analysis, I examined the impact on ICER of different healthcare professionals delivering CMR. The costs were adjusted to represent costs for different healthcare professions (nurses, pharmacists, doctors). Different levels of expertise were also analysed. The ICER was bigger than in the base-case analysis for the following professions: pharmacist specialist, pharmacist – advanced, pharmacist – team manager, pharmacist consultant, associate specialist and consultant: medical. The CMR was more cost-effective than in the base-case analysis when the intervention was delivered by registrar, hospital-based nurse, foundation doctor FY2 and FY1.

Figure 4.5 Tornado diagram: changes in structural assumptions on the healthcare professional delivering the CMR intervention



The lower the value of ICER, the more cost-effective CMR becomes.
Green – more cost-effective than base-case; red – less cost-effective than base-case.

The cost of ED reattendance

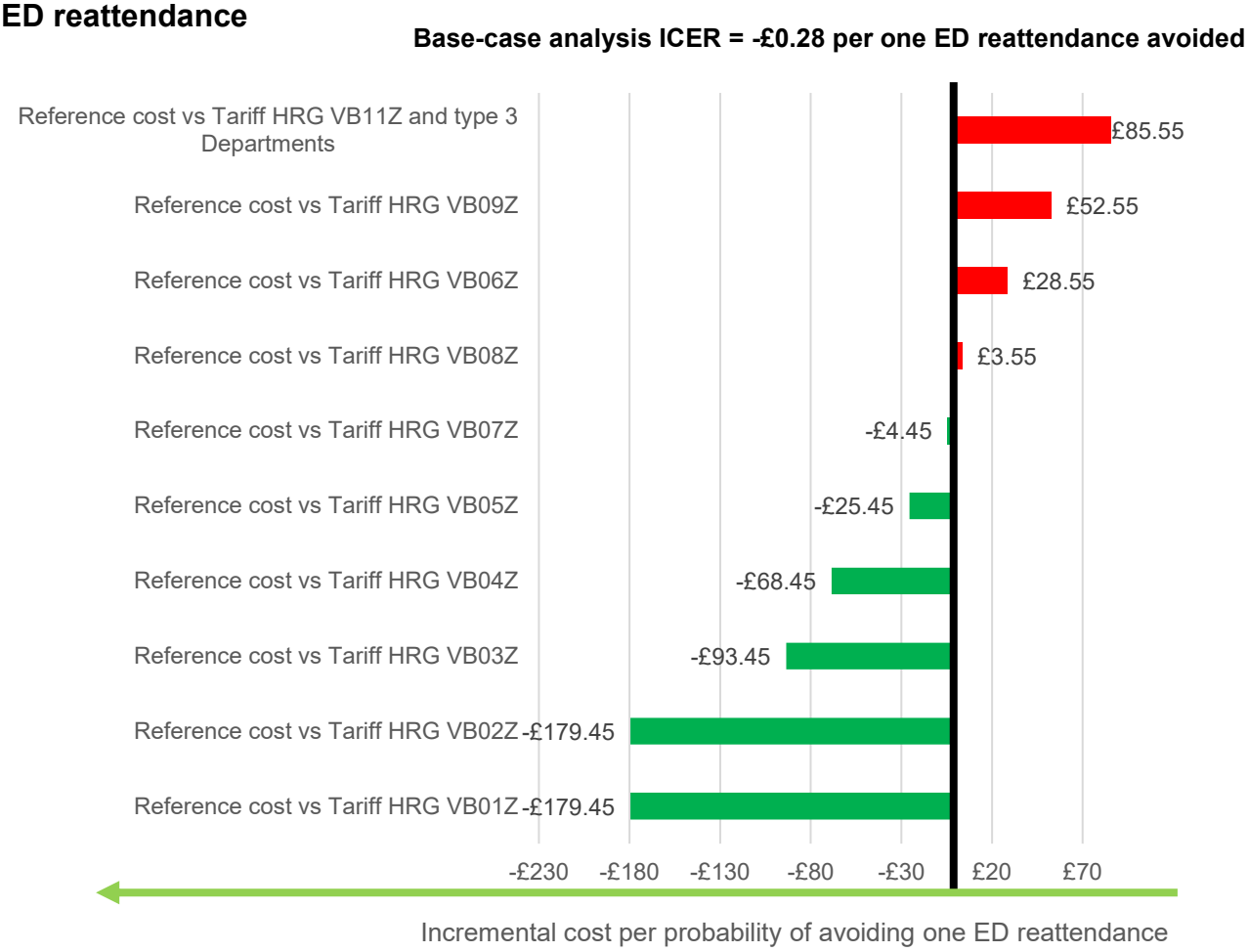
The uncertainty of the structural assumption to use reference cost for the base-case analysis was analysed in the deterministic sensitivity analysis. In the univariate sensitivity analyses the cost of ED reattendance was replaced with different tariffs associated with emergency medicine from the NHS National Tariff. Table 4.8 presents the HRG codes that were analysed in the sensitivity analysis. The least expensive investigation procedures at the emergency department with HRG codes VB06Z, VB07Z and VB09Z changed the ICER to a value above 0, whereas the tariffs for HRG codes VB01Z, VB02Z, VB03Z, VB04Z, VB05Z and VB07Z did not change the conclusion from the base-case analysis, which was that CMR dominated over usual care (figure 4.6).

Table 4.8 HRG codes from the National Tariff 2019-20

HRG code	HRG name
VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment
VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment
VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment
VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment
VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment
VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment
VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment
VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment
VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment
VB10Z	Emergency Medicine, Dental Care
VB11Z	Emergency Medicine, No Investigation with No Significant Treatment
VB99Z	Emergency Medicine, Patient Dead On Arrival

Source: (National Tariff Payment System, 2019)
HRG, healthcare resource group; the codes VB10Z - Emergency Medicine, Dental Care and VB99Z - Emergency Medicine, Patient Dead On Arrival were excluded from the analysis. The list of codes for treatment and investigation can be found in appendix A.

Figure 4.6 Tornado diagram: changes in structural assumptions on the cost of ED reattendance



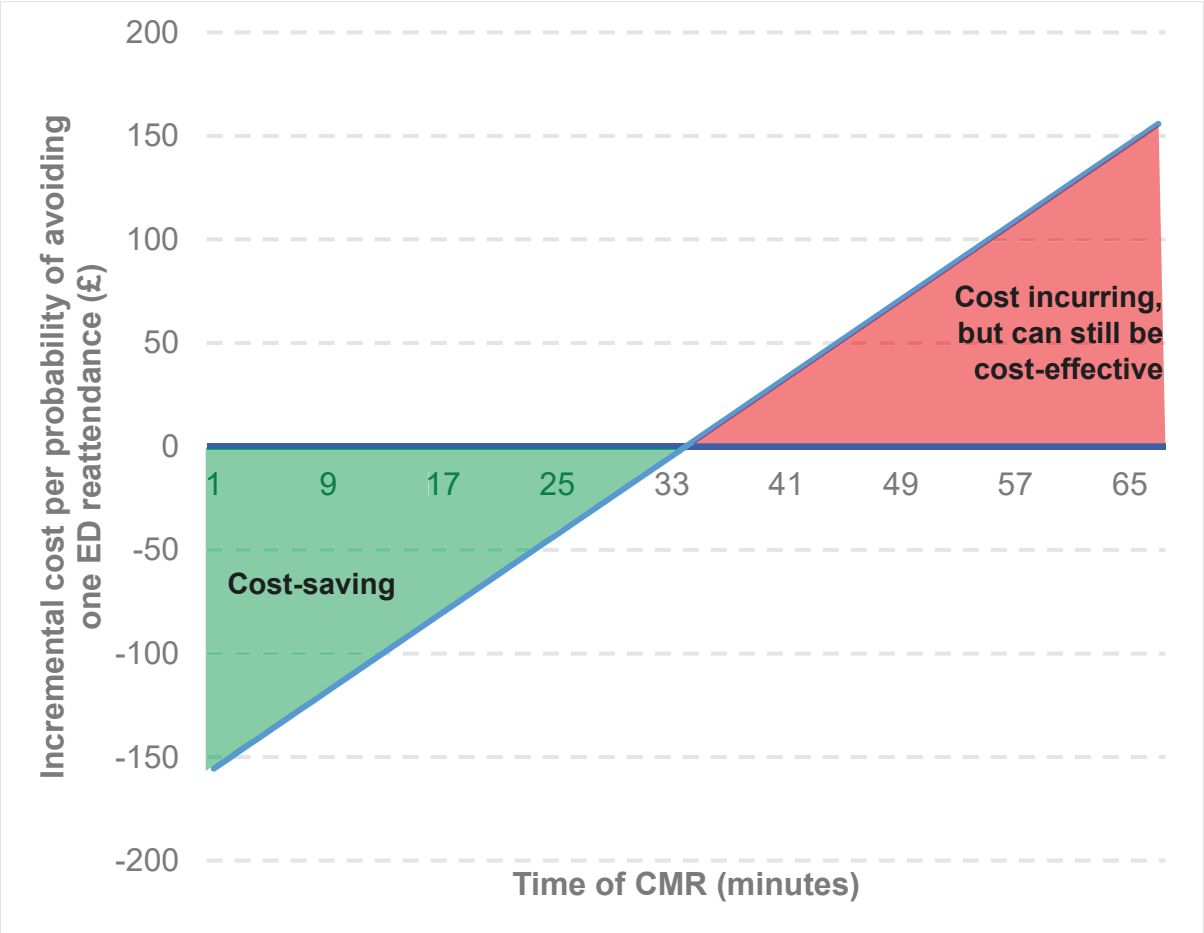
The lower the value of ICER, the more cost-effective CMR becomes.
Green – more cost-effective than base-case; red – less cost-effective than base-case.

Time to complete CMR

As described in chapter 2, CMR is a complex intervention that can be done in several ways. Therefore, even though evidence provides estimates of the average time needed to complete CMR, the time may vary depending on the local setting. This sensitivity analysis tried to address this uncertainty by providing estimates for ICER in relation to time needed to complete the intervention. This may allow local decision makers to investigate how much time they spent on CMR and by providing this information assess the probability of CMR being cost-effective in their local setting. Figure 4.7 presents the results of sensitivity analysis in relation to intervention time. From the perspective of the UK NHS, the CMR was cost-saving if the intervention took no longer than 33 minutes. If the intervention took longer than 33 minutes CMR was no longer cost-saving, however it could still be cost-effective.

This depends on the maximum willingness to pay of a decision-maker for the probability of avoiding one ED reattendance.

Figure 4.7 Deterministic sensitivity analysis: results in relation to time needed to complete the intervention

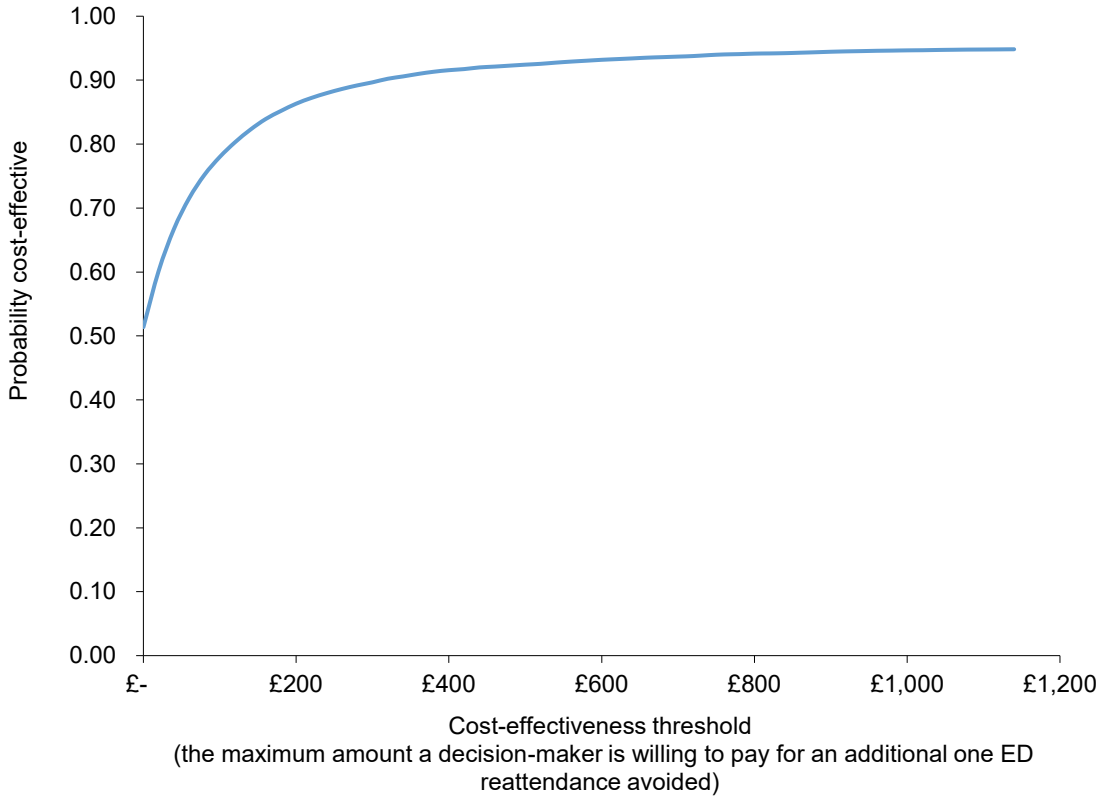


4.3.4 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was carried out with 10,000 second-order Monte Carlo simulations and the values were summarised in the form of a cost-effectiveness acceptability curve (figure 4.8). The curve represents the impact of uncertainty on the result of ICER in relation to the cost-effectiveness threshold of decision-makers' maximum willingness to pay (MWP) for an additional ED reattendance avoided. The probability of CMR being cost-effective increases as the MWP for one ED reattendance avoided increases. Even when the MWP equals £0, the probability of CMR being cost-effective is 51%. This increases to a probability of 80% if the MWP equals £117. The 95% probability that CMR will be a cost-effective

intervention compared with usual care is achieved when the MWP for ED reattendance avoided equals £1,290.

Figure 4.8 Probabilistic sensitivity analysis: cost-effectiveness acceptability curve



With 10,000 simulation iterations, the mean ICER was £4.53, with CMR on average providing 15% fewer ED reattendances with the increase in cost of £0.69. The results from PSA are summarised in table 4.9, where the mean values of cost and effects of CMR and usual care are presented.

Table 4.9 Probabilistic sensitivity analysis: average results from 10,000 simulations

Options	Cost	Probability of avoiding an ED reattendance	ICER
CMR	£95.04	0.56	£4.53 per ED reattendance avoided
Usual care	£94.35	0.41	
Difference between CMR and usual care	£0.69	0.15	

4.4 Discussion

This chapter explored the cost-effectiveness of CMR over a short-term (12-month) time horizon, compared with usual care for patients acutely admitted to hospital, from the perspective of the UK NHS. The study looked at a short timeframe and therefore a conservative assumption was made that there was no difference in QALYs, and the measure of benefit was the avoidance of ED reattendance. The results estimate that it was likely that CMR is a cost-effectiveness intervention, where even with cost-effectiveness threshold of £0 the probability of CMR being cost-effective was 51.37%.

4.4.1 Contribution to the field

Cost-effectiveness of CMR for the general elderly population

To my knowledge, there have been no previously published studies analysing the cost-effectiveness of pharmacist-led CMR in the UK NHS acute care setting. The published studies of cost-effectiveness of CMR in the UK are only focused on the community and primary care setting. The studies considered CMR carried out by a community pharmacist or GP at patients' homes, in a community pharmacy, or in a GP surgery. The cost of the intervention might differ significantly between a CMR carried out in hospital and one carried out in the community (e.g. travel cost of healthcare professional, difference in cost of pharmacist vs GP lead CMR etc.)

Moreover, the target population of patients who will receive the intervention differ. In my study the patients are older people who are acutely admitted to hospital and have high risk of readmission within 12 months after discharge. The population of patients in the current available evidence from UK literature are patients in better health who can receive the intervention in their own home or in a GP surgery or community pharmacy.

In chapter 1, nine studies looking at the health economic impact of CMR were identified (see section 1.3.3 'Literature about cost-effectiveness of medication review'). Six of the studies were based in a community setting and three in a hospital setting.

All three studies that looked at the economic impact of CMR carried out in hospitals, were conducted outside of the UK:

- Gallagher *et al*., 2016 – Irish study
- Ghatnekar *et al*., 2013 – Swedish study
- Wallerstedt *et al*., 2012 – Swedish study

In this discussion, I highlight the results from studies conducted outside the UK as general information about the cost-effectiveness of CMR. As previously mentioned in chapter 1, these results are not comparable, as the costs, the financing of the healthcare system and the cost-effectiveness threshold differ from country to country.

The two most recent studies (Gallagher *et al*., 2016; Ghatnekar *et al*., 2013) concluded that CMR was a cost-saving intervention, by providing more benefit at a lower cost compared to usual care. By contrast, in the Wallerstedt *et al*. (2012) study, the authors concluded that CMR was unlikely to be a cost-effective intervention in the hospital setting as, although CMR did provide QALY gain, it was too small to justify the cost. The results of my study are in line with the two most recent studies, where CMR is a cost-saving intervention that provides more health benefit at a lower cost.

Contrary to analysis of CMR conducted in hospitals, the results from cost-effectiveness studies of CMR delivered in a community setting show opposite

results. Two studies concluded that CMR was not cost-effective; three of the studies concluded that CMR was cost-incurring; and only one study, with potentially serious limitations, concluded that it was cost-saving.

This might suggest that CMR carried out in a hospital setting is more likely to be cost-effective compared to CMR carried out in a community setting. People who come to hospital are more likely to be on polypharmacy and have comorbidities, which would imply that they are more likely to need a CMR intervention. However, optimising the medicines already in the community might prevent these patients from going to hospital in the first place. Moreover, if medicines are optimised in the hospital setting and then later changed in the community this can lead to the patient again being at risk of readmission. Therefore, it is crucial that medicines optimisation is an integrated process with appropriate communication between primary, secondary, social and community care.

Which patients should receive CMR?

There are several guidelines which indicate who could be considered to be in the target population for CMR (Duerden *et al*., 2013; NHS Scotland *et al*., 2012; NICE, 2015a; Scottish Government Model of Care Polypharmacy Working Group, 2015; Scottish Government Polypharmacy Model of Care Group, 2018). The guidelines suggest that the target population is most likely older patients with long-term conditions, which matches the population of patients included in this study.

Therefore, the target population of patients who should receive CMR is very broad, which makes it challenging from a methodological point of view when conducting cost-effectiveness analysis.

The study conducted as part of this chapter tried to incorporate the economic impact for the whole target population of patients that should receive CMR. In the subgroup analysis of this study we see the results follow a logical pattern in which the older the patient group, the more cost-effective CMR is. Older people are more prone to be on polypharmacy and have a higher risk of reattendance to emergency department within 12 months of discharge. In the model we see that the cut-off point for CMR being cost-saving is 65 years. Intervention which is not cost-saving can still be

cost-effective, because we might want to pay for the additional health benefit associated with the intervention. This means that even though CMR may not be cost-saving for people below 65 years of age it can still be cost-effective.

Which healthcare professional should conduct CMR?

In the guide on medicines optimisation (NICE, 2015a) NICE suggests that organisations should determine locally the appropriate health professional to conduct CMR. That healthcare professional involved should have knowledge of managing medicines and therapeutic medicines use along with good communication skills.

In the base-case analysis of the cost-effectiveness model it is assumed that the pharmacist is delivering the intervention. In the deterministic sensitivity analysis, different structural assumptions, with other healthcare professionals delivering the intervention, were tested. The intervention was cost-saving if it was delivered by a pharmacist, registrar, hospital-based nurse or foundation doctor FY2 and FY1. It was cost-incurring, but still potentially cost-effective, if it was delivered by a pharmacist specialist, pharmacist – advanced, pharmacist – team manager, pharmacist consultant, associate specialist and consultant: medical.

A pharmacist delivering the CMR might be an appropriate option as pharmacists have the appropriate level of knowledge about medicines and the analysis found that CMR delivered by a pharmacist was likely to be cost-saving. However, the recommendation from this study would suggest considering using other healthcare professionals to deliver the service locally based on experience, knowledge and skills necessary for successful delivery of CMR. Based on locally established maximum willingness to pay, healthcare organisations can determine which healthcare professional would be well suited to deliver the intervention at an appropriate cost.

4.4.2 Contribution to thesis and implication for further research

The study addresses the gap in the literature by providing evidence for the cost-effectiveness of CMR in UK NHS acute care. The study indicates that a CMR

has the potential to be a cost-effective – or even cost-saving – intervention. The results from this chapter suggest that pursuing the analysis of long-term cost-effectiveness is worthwhile.

Incorporating the whole target population of patients who should receive CMR created some methodological compromises in the study, which I mention in the strengths and limitations section of this chapter. General population of patients limited the possibility to accurately determine the full care pathway for such diverse group. To address the limitations a more in-depth model would require narrowing down the target population for the analysis. This leads to chapter 5, in which the target population for more in-depth modelling is chosen and chapter 6, long-term cost-effectiveness analysis of CMR for the identified target population.

The recommendation for chapter 6 (long-term modelling of CMR) from this chapter is to use the patient health outcomes (quality-adjusted life year (QALY)) gained from CMR.

4.4.3 Strengths and limitations

This is the first cost-effectiveness analysis of pharmacist-led CMR in the UK NHS acute care setting. The study can provide valuable information for decision makers, healthcare providers and healthcare professionals regarding the value for money of completing a CMR for older people in acute care.

One strength of this study is that the target population of the analysis is the general population of older people in the UK, which means that the population in the analysis reflects the whole population of patients that CMR is aimed at. The population which can receive CMR in the UK comprises a very broad and diverse group of patients, with different conditions and varying severity of these conditions. This model tries to account for the whole diverse group, but also tries to unpack the group into sub-populations in the subgroup analysis. This study presents high-level findings for the whole diverse group of patients, whereas the study from chapter 6 of this PhD is targeted at a more specific target population, as outlined in chapter 5.

To assure external validity, the study is based on current best practice in health economic analysis. The relative treatment effect comes from a systematic literature review of the highest standard, the Cochrane review with meta-analysis (Christensen & Lundh, 2016). Systematic review and evidence synthesis assure that all the relevant evidence is incorporated. The baseline data come from a national registry in the UK, called the Hospital Episode Statistics (HES) dataset, which holds more than 200 million records (HERC Oxford University, 2019a), making the estimates of admissions in the model highly accurate.

Because CMR is a complex intervention which can vary depending on local context, the model tries to incorporate different methods of delivering the intervention. The model can be adjusted to represent different healthcare professionals delivering the intervention, which might be helpful when establishing the cost-effectiveness of CMR at a local level. The model also allows us to interpret results based on the time needed to complete the intervention, which can help decision makers at a local level to establish whether the CMR is likely to be cost-effective in their local setting.

Another strength of the study is extensive probabilistic and deterministic sensitivity analysis. The results of the sensitivity analysis indicate that the model was most sensitive to change in the structural assumptions. For example, when the effectiveness of CMR parameter was based on only one RCT (Lisby *et al*., 2010) rather than on the whole systematic literature review, CMR was least cost-effective. The RCT in question included only 100 patients and followed them for three months. The follow-up period and the sample size of the study could have had an impact on the results and important treatment effects could have been overlooked. In the base-case, which used synthesised evidence (systematic literature review of RCTs with meta-analysis) including the Lisby *et al.* study, CMR was a cost-saving intervention.

Because this is the first cost-effectiveness study of CMR in UK NHS acute care, it is not free from limitations.

Firstly, the model looks only at the short-term costs and effects associated with CMR. The available evidence of effectiveness of CMR includes studies with a short follow-up. In many previously published systematic literature reviews of effectiveness

of CMR, the conclusion is that the follow-up in the studies is too short. The Cochrane systematic review from 2016 mentioned that due to short follow-up of the studies included in the review (30 days to one year) important treatment effects could have been overlooked. In the review, the authors conclude that CMR may reduce the short-term outcomes of inappropriate prescribing, like the number of emergency department reattendances. High-quality studies with follow-up of at least one year are required to provide a more accurate estimate of the effect of CMR on long-term clinical outcomes such as readmissions and mortality (Christensen & Lundh, 2016).

This limitation was addressed as part of this PhD by developing a more in-depth economic analysis that models the effect of changes in prescribing on long-term outcomes. The long-term cost-effectiveness of CMR is analysed in chapter 6.

Secondly, the outcome measure which is defined as ED reattendance averted encompasses a lot of different health outcomes. The target population is a broad group, with different health needs and on different medication, which can lead to different causes of ED hospitalisation. That is why the severity of the condition for which the patient is reattending as well as the cost of the treatment received can vary.

In sensitivity analysis I tried to address that issue by using the National Tariff costs for all the possible treatment and investigation costs that the patient might receive in the emergency department.

Thirdly, in sensitivity analysis, because of a lack of empirical data, the difference in effectiveness of CMR delivered by different healthcare professionals was not analysed and only the costs were adjusted.

Finally, there were limitations relating to the aspects of complexity of CMR (from chapter 2) that could not readily be addressed. The experience and knowledge of the pharmacist conducting the review and engagement of the patient could have a major impact on the results of the analysis. The results could vary based on systemic issues of the specific healthcare provider (resources in place, time, availability etc.) and on the interaction between different parts of the healthcare system (e.g. communication about the changes in medicines regime between acute care and the community (GP, community pharmacy, nursing homes)) and between different

healthcare professionals (pharmacist, junior doctors, consultants, nurses, etc.). Furthermore, the exact nature and extent of usual care is dependent on each individual hospital, which causes variations in the relative risk of reducing emergency department reattendances by CMR between different sites.

4.5 Conclusions

The study demonstrated that pharmacist-led CMR has the potential to be a cost-effective or even cost-saving intervention within a 12-month time horizon for older people acutely admitted to hospital from the perspective of the UK NHS. The second-order Monte Carlo simulation carried out for 10,000 simulations indicated that there was a 51% probability of CMR being cost-effective if the cost-effectiveness threshold for one ED reattendance averted was £0. The probability increased to 80% when the threshold equalled £117.

Subgroup analysis found that the older the patient group, the more cost-effective CMR becomes. In the deterministic sensitivity analysis, it was determined that results were most sensitive to the effectiveness of CMR in reducing ED reattendances and to the cost of these reattendances.

When analysing structural assumptions of the model, I found that if CMR took no longer than 33 minutes it could be considered cost-saving. The most appropriate healthcare professional delivering the intervention should be determined locally, however there was a good indication that pharmacists might be the ‘sweet spot’ between having enough experience to deliver a good quality CMR and still being a cost-saving option.

The promising results suggested that pursuing the analysis of long-term cost-effectiveness is worthwhile. Long-term modelling should include estimating the potential gain in quality-adjusted life year (QALY) from CMR. To allow more in-depth cost-effectiveness modelling, narrowing down the target population is required.

CHAPTER 5 TARGET POPULATION

The purpose of this chapter is to answer research question number 4:

What are the target populations of patients acutely admitted to hospital who could benefit from CMR? Out of those, which population should be included in the modelling of long-term cost-effectiveness of CMR?

In chapter 4, I conducted a cost-effectiveness analysis for all acutely hospitalised NHS patients aged 65 years or older. While the results were promising, due to methodological challenges of analysing such a broad and diverse population of patients, the results only reflected a short-term (12-month time horizon) period and could not be linked to quality and length of life by measuring the QALY gain.

The conclusion from chapter 4 was that to explore the long-term cost-effectiveness of CMR it is essential to determine a narrower target population for analysis. The guidelines on medicines optimisation and polypharmacy, which I describe in this chapter, as well as studies that evaluated the effectiveness of CMR in hospital care, all suggest a very broad and diverse group of patients that could benefit from CMR. The patients described in the literature are usually older, experiencing frailty and suffering from multiple long-term conditions that are treated with multiple medicines. This group represents many of the patients requiring medical care in UK hospitals.

From an economic modelling perspective, it would be challenging to conduct a long-term cost-effectiveness analysis for such a large and diverse population. This is because each medical condition within the population has different treatment and management pathways. Building a model based on the NICE treatment pathway for such a diverse group might not be best health economic practice. This is because cost-effectiveness models need to be sufficiently sophisticated to capture the main aspects of a decision problem, but simple enough to provide results in a timely manner (Claxton *et al*., 2004; Weinstein *et al*., 2003).

Such a broad general population can receive a wide variety of medicines, all of which could potentially be important to include in the cost-effectiveness model. This again could make the model too complicated and thus make the results more uncertain. The same can be said about multiple outcome measures that would need

to be included in the model; evidence on the impact of deprescribing medicines is more likely to be disease specific.

By focusing the scope of cost-effectiveness of CMR on a single medical condition it is possible to reduce uncertainty around the results of the model and extend the time horizon used for the analysis to a lifetime horizon. It would also allow the results to be linked to the patient outcome measured (such as QALYs). Therefore, the aim of this chapter was to select one medical condition that could be set as a target population for long-term cost-utility modelling of CMR.

In this chapter, I first present the different target groups of patients that the current practice guidelines suggest should receive CMR. Then, I describe the methods used to narrow down the target population. Finally, I present the results from the analysis and recommend the final target population to be used as a base for the cost-utility model presented in chapter 6.

5.1 Background

The background section describes the target population for CMR published in medicines optimisation and polypharmacy guidelines. CMR is an intervention that could benefit a large group of patients, because the use of medicines in the population is high. It is estimated that an average person in England used 19 prescription items in 2013 (NICE, 2015a). Therefore, there have been attempts to identify a group of high-risk patients who would benefit most from CMR.

5.1.1 King's Fund

Polypharmacy and medicines optimisation: Making it safe and sound (Duerden *et al*., 2013)

The King's Fund tried to establish criteria for identifying patients with high-risk polypharmacy, but the report also noted that even patients with a low number of prescribed medicines are at risk of inappropriate polypharmacy. The criteria selected should serve as an indication of high-risk patients, rather than identifying all patients at risk.

King's Fund criteria are:

1) Patients who are on ≥ 10 regularly prescribed medications;
2) Patients who are on ≤ 9 and ≥ 4 regularly prescribed medications with one or more of the following criteria:
    a. Patients with potential drug on drug interaction or clinical contradiction;
    b. Patients with adherence problems
    c. Patients on end of life treatment or palliative care
    d. Patients on potentially inappropriate prescription (PIP)
    e. Patients who in the medical records do not have comorbidities, which might be an indication that there are too many medicines treating a single condition

5.1.2 The Scottish Government Polypharmacy Model of Care Group (SGPMCG)

Polypharmacy Guidance (Editions 1-3) (NHS Scotland *et al*., 2012; Scottish Government Model of Care Polypharmacy Working Group, 2015; Scottish Government Polypharmacy Model of Care Group, 2018)

The Polypharmacy Guidance has different but similar criteria for identifying patients who should be targeted for CMR compared to the King's Fund.

The guidance suggests that high-risk groups of patients who could benefit from CMR are frail patients, patients on polypharmacy and patients receiving high-risk medicines (with several publications cited describing what high-risk and potentially inappropriate medications are).

There were also two specific groups of patients highlighted as candidates for CMR:

1) Patients at care home facilities who are 50 years old or older, no matter how many medications they are on.
2) Patients aged 75 years old or older (depending on the availability of resources the group could be expanded to 65-74), on 10 or more medications, of which at least one is a high-risk medication and with high risk of readmissions and admissions.

The SGPMCG suggests further prioritisation based on local context:

1) Patients with comorbidities – it is estimated that in 2018, 2.9 million people lived with ≥ 3 long-term conditions. Although comorbidity is associated with age, the target population for CMR should include all age groups for patients with comorbidity.
2) Patients with frailty – these patients are recognised to have a clinical state of vulnerability, which does not have to be static, and the level of frailty can vary for the patient over time. Although age is a significant predicting factor of frailty, this group should not be limited by age. Frail patients are at risk of rapid decline in health condition if their medicines are not optimised, adverse drug events and drug-on-drug interactions.
3) Patients with a dominant condition – which means that the patients are recognised with a condition which affects decisions for all the other conditions, for example dementia.
4) Patients receiving end-of-life care – the risk versus benefit of prescribing certain types of medicines should be taken into account, as the comfort of patients at this stage is the priority.

5.1.3 The National Institute for Health and Care Excellence (NICE)

Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes (NICE, 2015a)

NICE published a guideline on Medicines Optimisation in which it recommends carrying out a CMR for a population of patients that have a clear indication of needing a CMR. The guidelines recommend conducting medication review for:

1) Patients suffering from chronic or long-term conditions
2) Older people
3) Patients on polypharmacy

5.1.4 Adopting guideline recommendation

All three guidelines suggest similar target patient populations who can benefit from CMR. The criteria used in the guidelines usually refer to the number of medicines, age, frailty, comorbidities and chronic conditions. The criteria used to establish the target population mentioned in the guidelines are too generic, which means that including all the patients that the intervention could help would not result in narrowing down the population in order to conduct a more targeted cost-utility analysis.

Guidelines were used as a starting point to explore a way to narrow down the target population. For the purpose of this chapter, the criteria for narrowing the target population were based on NICE guidance, which represents the recommended standard of care for patients in the NHS in England. Therefore, the population was narrowed down based on the age of patients, the presence of conditions which can be defined as chronic care conditions and patients likely to experience problematic polypharmacy.

5.2 Methods for selecting target population

Based on NICE guidance I developed a set of criteria to establish a population of patients who could potentially benefit most from CMR intervention. In principle, an economic evaluation of CMR for all disease areas would be the preferred choice, but as mentioned before, this was not possible. Therefore, a model was used to help identify a disease area for which CMR would probably generate the most value for money and where the intervention might have greatest effect. This links with the principles of welfare economic theory of optimisation of scarce resources, by obtaining social ordering over alternative possible states of the world (Boadway & Bruce, 1984; McIntosh *et al*., 2010).

The study was planned out in three stages:

5.2.1 Stage 1: Review of literature about problematic polypharmacy

Polypharmacy is the concurrent use of multiple medicines, which can be appropriate or problematic. Therefore, defining polypharmacy as problematic just based on the number of medicines prescribed to the patient is inappropriate. Defining problematic polypharmacy based on the number of medicines will also not help to narrow down the target population for the cost-utility model, as different patient cohorts are prescribed multiple medicines.

Instead, a different approach was adopted; to select the target population a review of literature was conducted to see what the most common negative consequences of polypharmacy are. Conditions associated with the highest number of adverse effects of polypharmacy will be selected for the analysis.

5.2.2 Stage 2: Four-domain model for selecting target population

To select the target population the following steps were undertaken.

The first step was to compose a four-domain model for selecting the target population. The domains were selected based on NICE guidelines on Medicines optimisation (NICE, 2015a) supplemented by information about the public health importance of the medical condition. For each of the four domains, criteria for measurement were selected.

The four domains with key measures for choosing the target population are listed below:

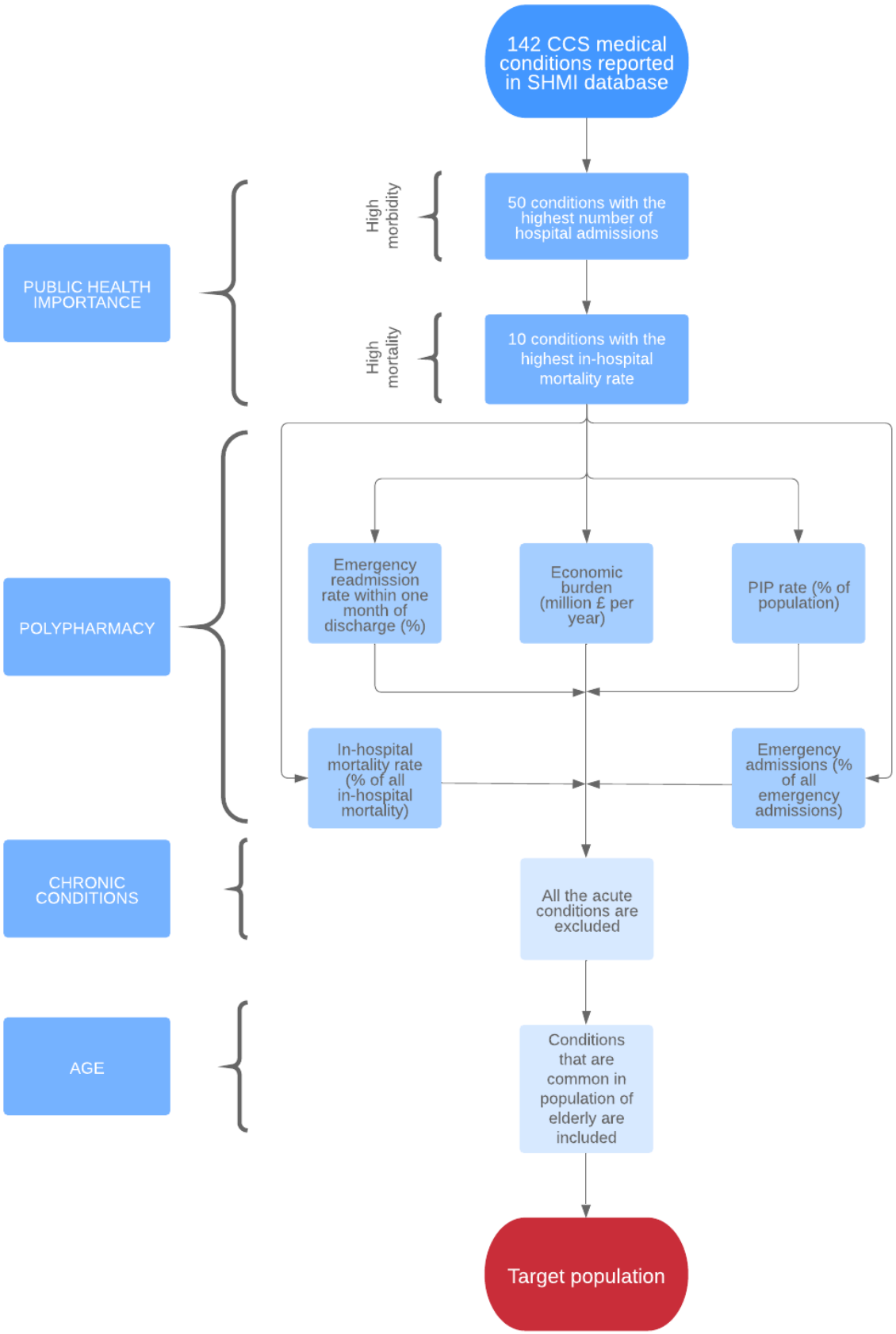
1. Public health importance of the medical condition:
   Key measures:
   - Admission rate
   - In-hospital mortality rate
2. Polypharmacy (based on information from review done in stage 1):
   Key measures:
   - In-hospital mortality rate (as in domain one)

- Emergency admission rate
- Emergency readmission rate within one month
- Economic burden
- Potentially Inappropriate Prescribing (PIP) rate

3. Chronic conditions:
   Acute conditions were excluded from the analysis
4. Age:
   An elderly population was selected

The decision model is presented graphically in figure 5.1. The starting point of the model is looking at all medical conditions from the Summary Hospital-level Mortality Indicator (SHMI) publications, which I describe in the section ‘Routinely collected data’ of this chapter.

Figure 5.1 Four-domain model for selecting target population



CCS – Clinical Classification System; SHMI – Summary Hospital-level Mortality Indicator; PIP – potentially inappropriate prescribing

The second step included exploration of available sources of data that provide information about key measures for each domain in the model. A variety of data sources were used to provide variables for the model. The sources of data can be classified into two main categories: routinely collected NHS data and data from a literature search of published articles and grey literature (reports of NHS organisations).

The final step was mapping and analysis of the evidence against the criteria and domains of the model.

5.2.2.1 Routinely collected data

The data about mortality and hospital utilisation come from national statistics published quarterly by NHS Digital in the SHMI (NHS Digital, 2018d). The SHMI reports on in-hospital mortality and admission to hospitals at a trust level in the English NHS. The SHMI provides a ratio between the observed deaths at trust level and the projections based on average England figures including characteristics of the patient population. The data include all the in-hospital deaths and deaths within 30 days post discharge of patients admitted to non-specialist acute trusts.

Both the admission data and the mortality data are coded using the Clinical Classification System (CCS) diagnostic groups. The CCS was developed for the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ). CCS is a categorisation scheme of diagnoses and procedures that is based on the World Health Organization's International Classification of Diseases, Revision 10 (ICD-10) (Wier *et al*., 2011).

All the ICD-10 diagnoses and procedures are incorporated in the lower number of clinically meaningful CCS codes. There were 140 CCS groups in the SHMI for data from the 2013-2017 period and since 2018 two new categories have been added, bringing the total to 142 CCS categories.

The data about emergency admissions come from published analysis of routinely collected hospital administrative data (Aylin, Yunus, Bottle, Majeed & Bell, 2010).

5.2.2.2 Targeted literature review

A targeted literature review was conducted to find data for 10 conditions that were identified as the conditions with the highest public health importance. Data were sought about:

- Emergency readmission rates within one month of discharge
- Economic burden
- Potentially inappropriate prescribing (PIP) rate

A comprehensive electronic database search was carried out on the Embase MEDLINE database, supplemented by a grey literature search through Google Scholar of NHS reports, national audits, and other public and private reports on the topic. The search was conducted in January 2018 and updated in July 2019, to ensure the most up to date evidence was included. The search was conducted using keywords relating to the three criteria mentioned above. To learn more about the key words and search strategy, please read Appendix B.

Inclusion and exclusion criteria

Overall

The review included studies that looked at UK adult population level data, published in English. For studies about economic burden and emergency readmission rate only UK data were included, but for the studies about PIP rate, data for other countries were included due to lack of UK-specific evidence. The studies were excluded if they looked only at the child population, or a subset of the population. Expert opinion and authors' reply were excluded from the analysis. The studies which provided estimates of economic burden, emergency readmission rate or PIP rate for multiple medical conditions combined were also excluded from the analysis.

Emergency readmission rates

Evidence looking at emergency readmission rates for any of the 10 medical conditions was included in the review if it provided data about emergency readmission within one month of discharge from the index admission. The one month period could be 28 days or 30 days, depending on the study. The studies were excluded if they looked at readmission rates following a specified intervention,

were case studies or looked at impact of different risk factors on readmission. Methods studies that concentrated on different approaches to measuring readmission rates were also excluded from the review.

Economic burden

The studies about economic burden of any of the 10 medical conditions were included if they provided estimates of the direct or indirect annual cost of the medical condition (or a combination of the two) for the UK NHS. Case studies, cost-effectiveness analysis of interventions, randomised control studies, costing studies, budget impact analysis, HTA submissions and all other types of studies that did not look at the economic burden of the medical condition for the whole population were excluded from the analysis. Studies which looked at the subset of direct or indirect costs were excluded from the analysis. Studies which looked at the mean cost per patient instead of the economic burden for the whole population were also excluded from the review.

PIP rates

Studies about PIP rates for the 10 conditions were included if the PIP rates were measured by a standardised tool for evaluating the quality of prescribing. To allow comparability between the conditions only PIP rates measured by the two most common tools: STOPP/START criteria or Beers criteria (with allowed modifications) were included in the review.

Data collection and data extraction

The studies were screened and selected based on the inclusion and exclusion criteria and evidence was extracted into a spreadsheet designed in Microsoft Excel.

Emergency readmission rates

For the studies looking at emergency readmission rates, the year of data collection in the study was presented. The data for emergency readmissions relate to patients who experience any all-cause, emergency admission within 28 or 30 days of discharge from an indexed admission and are presented as the percentage of all discharged patients from the studied population.

Economic burden

For the economic burden the following information was collected: the year to which data refers, direct healthcare costs, indirect healthcare costs and the total economic burden. The direct healthcare costs relate to costs of primary and secondary care, costs of medicines and costs of treating complications. The indirect costs relate to lost productivity due to hospitalisation or mortality associated with the medical condition. In some studies, they also reflect the costs associated with reduced quality of life and litigation costs.

PIP rates

Evidence about PIP rates was collated into a table with the year of the data collection, the rate of PIP (percentage of patients with at least one PIP in the population), the tool used to measure the PIP rate and the size of the population.

5.2.3 Stage 3: The final choice of one target population based on the four-domain model

Medical conditions that filled the criteria set out in the four-domain model (conditions left after the decision process described by figure 5.1) were presented as the candidate conditions that could be used for long-term cost-utility analysis of CMR in a hospital setting. Based on a literature search about the candidate conditions and current national and international guidelines about the management and treatment of conditions the following was reported:

- Definition
- Epidemiology
- Diagnosis
- Treatment and management
- Symptoms
- Prognosis

The final choice of a single condition was based on the criteria from the four-domain model that included: in-hospital mortality rate, emergency admission rate, emergency readmission rate within one month, economic burden and potentially inappropriate prescribing rate.

5.3 Results

5.3.1 Stage 1: Review of literature about problematic polypharmacy

Polypharmacy has been defined in various ways. A systematic literature review of the definitions has identified 138 different definitions of polypharmacy (Masnoon, Shakib, Kalisch-Ellett & Caughey, 2017). The common element for most definitions is: "the concurrent use of multiple medication items by one individual" (Duerden *et al*., 2013), but the term 'multiple' has various meanings in literature ranging from at least two to at least eleven medicines. Most studies (46.4%) used five medications daily as the cut-off point for polypharmacy, but more than half of the studies used a different definition, which can create variations in interpretation of data when examining polypharmacy (Masnoon *et al*., 2017).

The King's Fund has defined problematic polypharmacy as:

"the prescribing of multiple medications inappropriately, or where the intended benefit of the medication is not realised" (Duerden *et al*., 2013)

Problematic polypharmacy can have negative consequences in terms of number of potentially inappropriate prescriptions, in-hospital mortality, hospital admissions, hospital readmissions and increased treatment cost.

5.3.1.1 Potentially inappropriate prescribing

Potentially inappropriate prescribing (PIP) is also known as inappropriate medication use (IMU), inappropriate drug use (IDU) and inappropriate prescribing (IP). PIP is a practice of suboptimal medicines use that includes over-, under- and mis-prescribing of medicines (Parsons, 2017). PIPs can also refer to medicines where the risk outweighs their potential benefits, especially if there are more appropriate medicines available (Renom-Guiteras, Meyer & Thürmann, 2015). PIP can lead to increased risk of avoidable ADRs, admissions, readmissions, morbidity and mortality (Parsons, 2017).

Many studies report the correlation between polypharmacy and PIPs. One study conducted in 8 European countries (including the UK) found that PIPs were associated with polypharmacy with the relative risk of RR, 1.91 (95%CI, 1.62- 2.22) (Fialová *et al*., 2005). Another study conducted in Spain reported that the number of medicines prescribed for patients discharged from hospital was associated with PIP. This was most notable for patients who received at least three medicines and increased with a rate of 14-15% for each additional medicine prescribed (Hudhra *et al*., 2016). There is a growing body of evidence for the high prevalence of PIPs in the general population. Key risk factors for PIPs are: polypharmacy, depression, age, poor economic situation and living alone (Blanco-Reina, Encarnacion Ariza-Zafra, Ocana-Riola & Leon-Ortiz, 2014; Fialová *et al*., 2005; Fu *et al*., 2007; Gallagher *et al*., 2011; Gallagher *et al*., 2008; Galvin *et al*., 2014; García-Gollarte, Baleriola-Júlvez, Ferrero-López & Cruz-Jentoft, 2012; Gosch, Wörtz, Nicholas, Doshi, Kammerlander & Lechleitner, 2014; Hamilton, Gallagher, Ryan, Byrne & O'Mahony, 2011; Hill-Taylor *et al*., 2013; Motter *et al*., 2018; O'Mahony *et al*., 2015; Opondo *et al*., 2012; Parsons, 2017; Shade, Berger & Chaperon, 2014; Spinewine *et al*., 2007; Tommelein, Mehuys, Petrovic & Somers, 2015; Vezmar Kovačević *et al*., 2014).

PIPs can be measured using several tools described in the literature. These were developed to assess the appropriateness of medications and most were designed by expert panels consisting of pharmacists and geriatricians. A recent systematic literature review identified 36 different tools that were used to assess the appropriateness of medication therapy (Motter *et al*., 2018). Of the 36 tools, 23 were aimed at a general population of individuals aged 65 years or older. The lists of PIPs were mainly validated using the Delphi or modified a Delphi method, techniques used for achieving consensus among experts. The Delphi method requires experts to answer the same series of questions over a few rounds. The time between rounds is used by experts to reflect on the group's collective expert opinion and resolve any disagreement. One of the challenges of developing PIP tools for a general population of elderly patients is the known fact that older people are often excluded in efficacy and safety studies and are therefore underrepresented. The most common medicines mentioned in the list of 36 tools were benzodiazepines and non-steroidal anti-inflammatory drugs (NSAIDs).

Depending on the method of measurement, the prevalence of PIPs in the general population ranges from 21% to 79% (Riordan *et al*., 2018). In the UK in 2007 the prevalence of PIP (measured by STOPP/START criteria) based on 1,019,491 patient records from the Clinical Practice Research Datalink (CPRD) database was 29%.

5.3.1.2 Hospital admission

Several UK studies show a relationship between hospital admission and polypharmacy. A study conducted in Liverpool involving 3,695 patient episodes indicated a strong correlation between hospitalisation for adverse drug reactions (ADR) and the number of medicines used by a patient (Davies *et al*., 2009). The average length of hospital stay for patients with ADR was 20 days compared to eight days for patients without ADR. ADRs are associated with increased risk of avoidable admissions to hospital as half of ADRs that lead to hospitalisation are avoidable or potentially avoidable (Davies *et al*., 2009).

Meta-analysis of 42 studies, including three UK studies, reported that admission due to ADR as a percentage of all admissions was 8.7% (95% CI 7.6; 9.8). The 14 studies that reported data for the most common medicines implicated in ADR requiring admission to hospital highlighted that the most common medicines are:

- ACE inhibitors (5.5% - 23.4%)
- Antibiotics (1.1% - 22.2%)
- Anticancer drugs (1.5% - 9.1%)
- Beta-blockers (1.8% - 66.7%)
- Calcium entry blockers (1.0% - 8.3%)
- Digoxin (1.6% - 18.8%)
- NSAIDs (2.5% - 33.3%)
- Opioids (1.5% - 18.8%)
- Oral anticoagulants (3.3% - 55.6%)
- Oral antidiabetics (4.5% - 22.2%)

(Oscanoa, Lizaraso & Carvajal, 2017)

Data from 18,820 patients from England suggest that ADRs account for 6.5% of hospital admissions (Pirmohamed *et al*., 2004), whereas severe ADRs account for 5-17% of hospital admissions for older patients (Duerden *et al*., 2013).

A UK study based on data from Hospital Episode Statistics found that in the period between 1998 and 2005 there were 447,071 ADRs in a hospital setting with an increase of 45% over the seven years. The ADR predominantly occurred in patients aged 60 years old or older (59%) (Patel *et al*., 2007).

ADRs have a significant impact on public health by decreasing length of life, quality of life and increasing the costs of healthcare. Hospitalised patients can experience two types of ADRs:

1. ADRs that are the cause of admission to hospital
2. ADRs that occur during the hospital stay

Meta-analysis of 39 studies done in the USA on approximately 62,500 patients indicated that the incidence of serious ADR was 6.7%. Patients from category 1 (patients that were admitted to hospital because of ADR) were 4.7% of all patients. The remaining 2.1% were patients in category 2, patients that experienced ADR while in hospital (Lazarou, Pomeranz & Corey, 1998).

Wiffen *et al.* estimated that in the NHS England admissions due to ADR are responsible for 1.6 million bed-days, four out of 100 bed-days are treating people with admission due to ADR. A combination of ADR and hospital acquired infection increases the bed-days from four to 10 out of 100 (Wiffen, Gill, Edwards & Moore, 2002).

5.3.1.3 Hospital readmission

Readmission to hospital is recognised problem and contributes to the increased demand on secondary care. Patients with comorbidity are more likely to be readmitted (Bottle, Aylin & Bell, 2014) and patients with comorbidity are more likely to be on multiple medications.

There are several studies that look at the impact of polypharmacy on readmissions. One study published in 2018 was a multicentre cohort study of 25,190 patient records. The authors concluded that polypharmacy was associated with increased 30-day readmission to hospital. Each medication increased the risk of readmission with an odds ratio of 1.04 (95% CI 1.03; 1.05) (Basnet *et al*., 2018). A study from 2013 reached the same conclusions. A retrospective analysis of 414 patient records

concluded that polypharmacy was associated with 30-day readmission to hospital (Sehgal *et al*., 2013).

The readmissions are also associated with ADR. A systematic literature review that included 19 studies looked at prevalence of readmissions to hospital due to problems related with medicines. The prevalence ranged from 3% to 64% with median 21% and the first and third interquartile ranges 14% and 23% respectively (El Morabet *et al*., 2018). In the UK NHS a study estimated that ADRs directly contribute to around 20% of readmissions to hospital within one year of discharge (Davies *et al*., 2010).

5.3.1.4 In-hospital mortality

Polypharmacy is associated with an increased mortality risk. Evidence from a systematic literature review and meta-analysis of 47 studies show a significant association between polypharmacy and death with OR = 1.08 (95% CI 1.04; 1.12). The greater the number of medicines the patient is on, the higher the risk of death (Leelakanok, Holcombe, Lund, Gu & Schweizer, 2017). Table 5.1 presents the odds ratio for increased mortality risk dependent on the number of medicines that patients were using.

Table 5.1 The increased risk of mortality based on the number of concurrently used medicines

No. concurrently used medicines	Odds ratio of increased mortality risk
1-4	1.24 (95% CI 1.10; 1.39)
5	1.31 (95% CI 1.17; 1.47)
6-9	1.59 (95% CI 1.36; 1.87)
>10	1.96 (95% CI 1.42; 2.71)

CI, Confidence Interval. Source: (Leelakanok *et al*., 2017).

The obvious reason for increased risk of mortality for patients on polypharmacy is that they are using multiple medicines to treat their multiple comorbidities and therefore they are much frailer and at risk of mortality because of the disease burden.

However, this is not the only explanation, because polypharmacy is linked with an increased number of ADRs, which are linked with increased in-hospital mortality. There is evidence of an increased risk of ADRs the greater the number of medicines prescribed (Davies *et al*., 2009; Duerden *et al*., 2013; Gallagher *et al*., 2011). People admitted to hospital because of ADR have a high risk of in-hospital mortality. One in 20 people admitted to hospital because of ADR die in hospital, which was estimated to account for 26,399 in-hospital deaths in the UK between 1999 and 2009 (Wu *et al*., 2010). Some suggest this is an underestimate due to underreporting.

5.3.1.5 Cost of treatment

Drug treatment costs are an important contributing factor to overall health spending in the UK. In the financial year 2012/13, expenditure on hospital medicines alone was over £9.15 billion, which represents more than 50% of total NHS medicines expenditure (NHS Digital, 2018c).

NICE estimated that a reduction in admissions due to avoidable ADR could save the NHS up to £530 million per year (NICE, 2015b). In 2018, a systematic review based on 18 studies looked at the economic burden of ADRs in the USA and Western Europe (Formica *et al*., 2018). The authors found that the cost due to preventable ADR per one hospitalisation was between £2,529 and £7,996[4]. The excess length of stay (LOS) reported in the review was between 4.2 and 13 days (depending on the study). For the outpatient setting the cost was between £154 and £7,553[4], with LOS for patients who were subsequently admitted to hospital between seven and 9.3 days. Studies that reported the outcomes for both the inpatient and outpatient settings presented the combined cost of preventable ADR, which ranged from £57 to £2,414[4] and the mean LOS was 8.5 days in all settings. There were three studies (Dennehy, Kishi & Louie, 1996; Gyllensten *et al*., 2014; Leendertse *et al*., 2011) that estimated the indirect cost of ADR to be between £783 and £11,402[4] depending on the type of costs included in the calculation. For indirect costs, one study looked at productivity costs (absenteeism and presenteeism at work) and production costs lost (Leendertse *et al*., 2011); another study looked at indirect costs for hospital services

[4] The costs in (Formica *et al*., 2018) were presented in EUR. For the purpose of this chapter the costs were converted using the Bank of England exchange rate from January 2018; 1 EUR = 0.8870 GBP.

such as laundry and food (Dennehy *et al*., 1996); while (Gyllensten *et al*., 2014) looked at societal costs.

There is additional economic burden described that is associated with polypharmacy and which relates to the economic impact of medication errors (ME). “A ME is a preventable event that may lead to inappropriate medication use or patient harm” (Elliott *et al*., 2018). MEs are frequent, often avoidable and represent a major threat to patient safety (Schachter, 2009). It is estimated that in England there are 4.8 million errors each year, which can lead to severe harm for the patient (Elliott *et al*., 2018). Intervention of pharmacists can prevent consequences from many of these errors (Schachter, 2009).

The economic burden of ME consists of three elements:

1. The incidence of ME
2. The resources used connected with ME
3. The health effects of ME

(Elliott *et al*., 2018)

Two recent systematic literature reviews describe the economic impact of ME. The first (Walsh *et al*., 2017) identified 16 studies. A subsequent review by Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU) (Elliott *et al*., 2018), which used the same search criteria but limited the search to UK studies, included four studies.

There was a notable difference in the estimates for cost of ME for different studies included in both reviews. The difference was due to disparity in methodology, which resulted in studies measuring costs of different things. In some studies, the low cost of ME was due to limiting the outcomes to simple errors, like ME for inhaler medication. In studies where the costs of ME were extremely high, the authors looked at litigation claims for ME for anaesthetic procedures. Therefore, the authors conclude there is a lack of good quality studies which could estimate the real economic burden of ME in the UK.

The average cost per ME in the (Walsh *et al*., 2017) review was between £2 and £99,102[5] and in the (Elliott *et al*., 2018) review, the cost ranged from £60 to £6.14 million[5].

5.3.2 Stage 2: Four-domain model for selecting target population

5.3.2.1 Domain 1: Public health importance

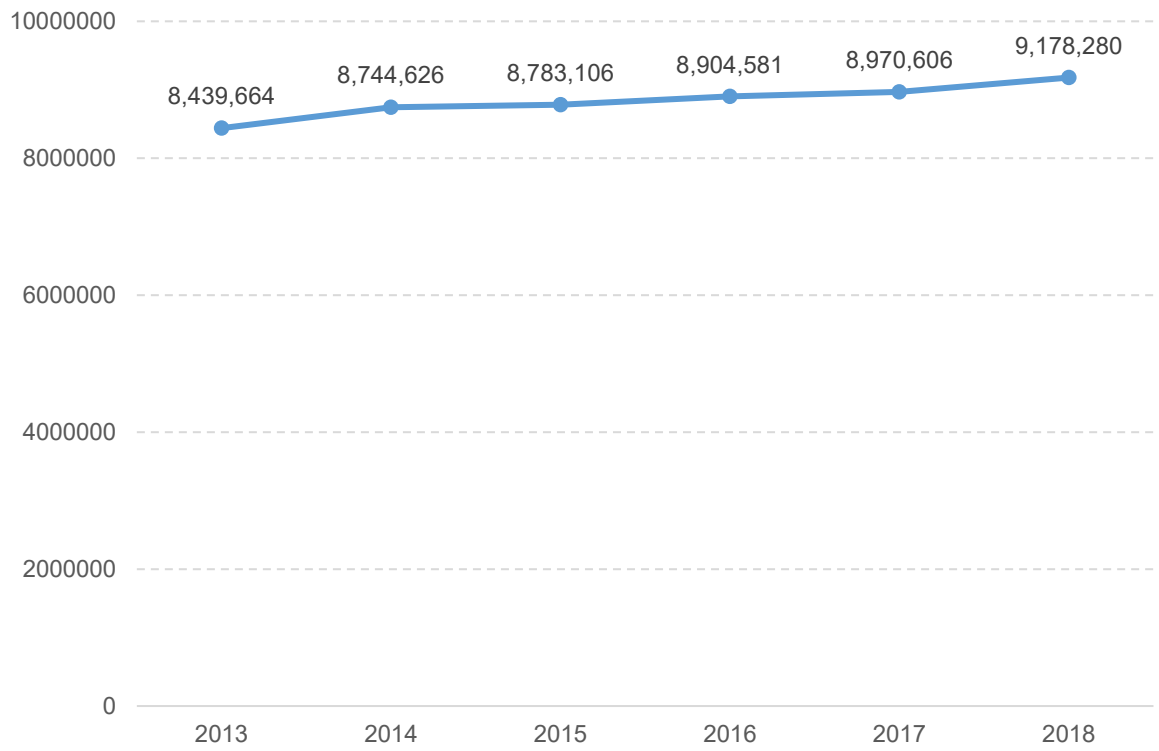
To determine the conditions with the highest public health impact, I extracted data from the SHMI dataset for the years 2013 to 2018 and grouped them according to the diagnostic group. The data are based on HES data and come from 141 UK NHS trusts, with 113,762 grouped admission and in-hospital mortality records for 142 medical conditions.

High morbidity

The data show that the number of admissions to UK NHS hospital trusts from 2013 to 2018 has increased with each year (figure 5.2). In 2013, the data reported 8,439,664 spells for 141 NHS trusts from which the data were collected. In 2018, the number of spells was 9,178,280 for 130 NHS trusts from which the data were collected. The number of trusts reduced over this period due to hospital trust mergers rather than a reduction in hospital sites.

[5] The costs in (Elliott *et al*., 2018; Walsh *et al*., 2017) were presented in EUR. For the purpose of this chapter the costs were converted using the Bank of England exchange rate from January 2018; 1 EUR = 0.8870 GBP.

Figure 5.2 Number of spells in the UK NHS between 2013 and 2018



Source: Author's analysis of the SHMI dataset for the years 2013 to 2018 (NHS Digital, 2018d)

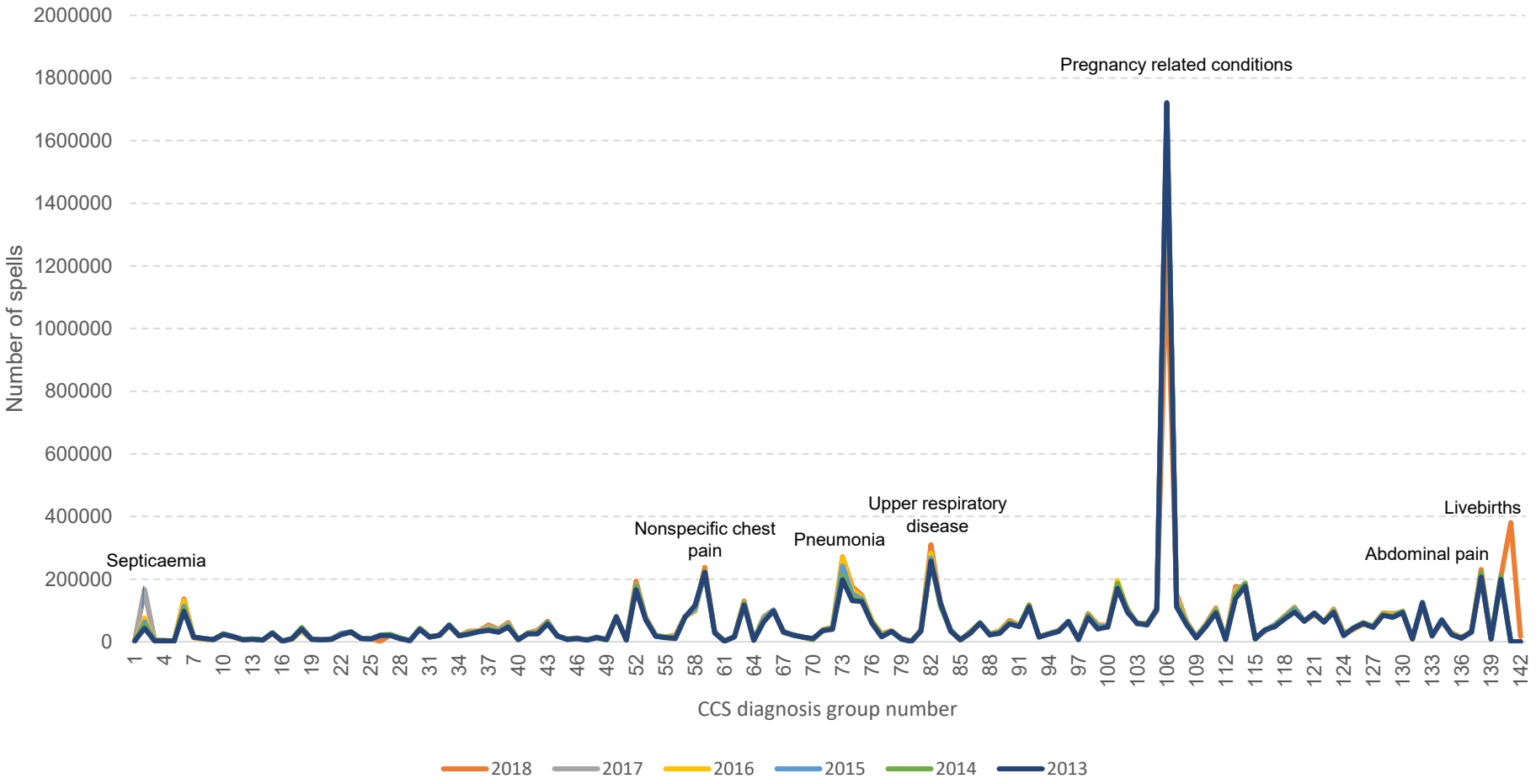
Figure 5.3 presents data about the number of hospital spells for years 2013 to 2018 by diagnostic groups. The most common causes of admission to hospital were pregnancy related conditions, livebirths, upper respiratory diseases, pneumonia, abdominal pain, nonspecific chest pain.

The data show a constant number of spells for most of the diagnostic groups with a low variation in the numbers. The biggest variation was a significant increase in the diagnostic group 'livebirths', however this is due to the fact that in 2013 there were only 140 CCS diagnostic groups and livebirths were coded as part of the diagnostic group 'pregnancy related conditions'. Since 2018 there have been 142 CCS diagnostic groups with the addition of two new diagnostic groups, 'livebirths' and 'non-Hodgkin's lymphoma'. Other conditions that noticed the biggest increase were 'septicaemia', from 42,924 spells in 2013 to 165,065 spells in 2018, and 'pneumonia', which more than tripled in the number of spells reported from 73,355 spells in 2013 to 270,955 spells in 2018.

The conditions which saw the biggest decrease were ‘pregnancy related conditions’ and ‘Hodgkin's disease’, which was due to coding issues with the addition of two new CCS groups. The number of spells for ‘coronary atherosclerosis and other heart disease’ also decreased from 116,305 spells in 2013 to 98,475 spells in 2018.

The top 50 CCS diagnostic groups by number of hospital admissions were selected to represent high morbidity of the medical condition. Out of these 50 conditions one will be selected as the target population for the long-term cost-utility analysis of CMR. All 50 conditions are presented in table 5.2 alongside data about the number of spells that were recorded in the most recent data for the period between February 2018 and January 2019.

Figure 5.3 Number of hospital spells by CCS diagnostic group in the UK NHS between 2013 and 2018



Source: Author's analysis of the SHMI dataset for the years 2013 to 2018 (NHS Digital, 2018d)

Table 5.2 Top 50 CCS diagnostic groups by number of spells in UK NHS trusts for the reporting period between February 2018 and January 2019

Medical condition		Diagnosis group number	Number of spells
1	Pregnancy related conditions	106	1,621,635
2	Upper respiratory disease, diseases of mouth (non-dental)	82	311,040
3	Pneumonia (excluding TB/STD)	73	270,557
4	Nonspecific chest pain	59	229,729
5	Abdominal pain	138	224,820
6	Allergic reactions, aftercare and screening, R codes	140	193,443
7	Ear and sense organ disorders (excluding TB/STD)	52	188,169
8	Septicaemia (except in labour), shock	2	178,518
9	Other connective tissue disease	113	174,414
10	Rheumatoid arthritis related diseases, acquired deformities, bone disease	114	170,936
11	Acute bronchitis	74	169,493
12	Urinary tract infections	101	165,666
13	Skin and subcutaneous tissue infections	107	150,867
14	COPD and bronchiectasis	75	147,399
15	Non-HIV related infections	6	131,228
16	Cardiac dysrhythmias	63	127,694
17	Poisoning	132	119,855
18	Intestinal infection	83	117,999
19	Biliary tract disease	92	110,881

20	Other perinatal conditions	119	106,570
21	Back problems, osteoporosis	111	105,520
22	Diseases of kidneys and ureters, bladder and urethra	102	104,491
23	Joint disorders, fractures and sprains	123	103,067
24	Acute cerebrovascular disease	66	101,437
25	Coronary atherosclerosis and other heart disease	58	97,955
26	Female genital/reproductive disorders	105	96,594
27	Superficial injury; contusion	130	92,873
28	Complication of device, implant or graft	128	90,282
29	Complication of surgical procedures or medical care	129	87,981
30	Other gastrointestinal disorders	98	87,953
31	Fracture of upper limb	121	85,541
32	Acute myocardial infarction	57	81,448
33	Birth-related conditions	118	80,370
34	Congestive heart failure; non-hypertensive	65	79,292
35	Epilepsy; convulsions	50	78,722
36	Other nervous system disorders	53	77,256
37	Fracture of neck of femur (hip)	120	66,793
38	Digestive, anal and rectal conditions	90	66,250
39	Asthma	76	65,928
40	Fracture of lower limb	122	64,670
41	Skin disorders	108	64,663
42	Syncope	134	63,723
43	Gastrointestinal haemorrhage	96	63,221

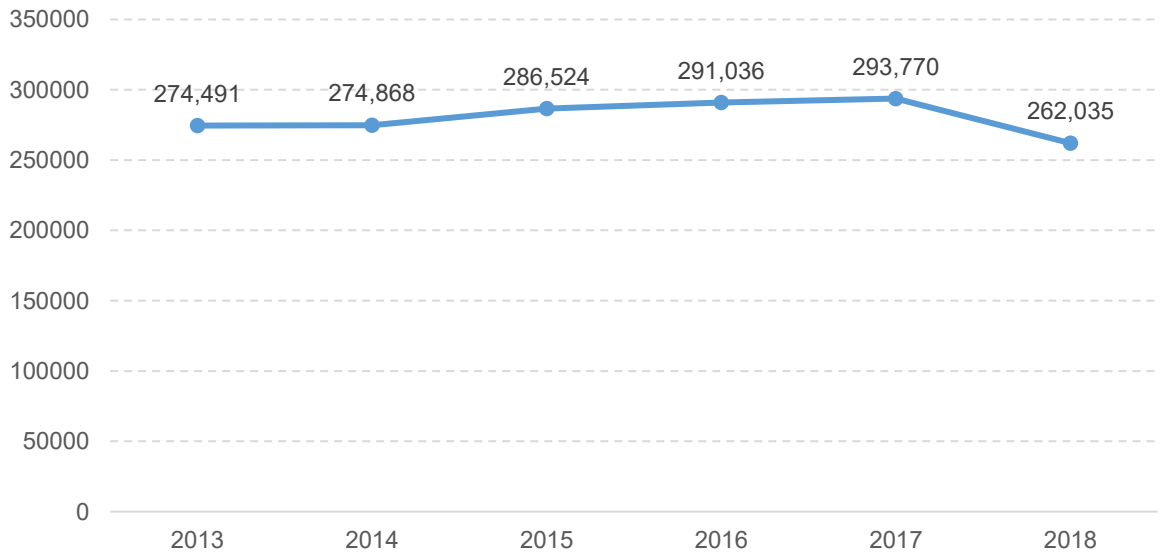
44	Non-organic mental disorders, anxiety	43	62,984
45	Anaemia	39	60,191
46	Abdominal hernia	87	58,669
47	Male genital disorders	104	58,297
48	Genitourinary symptoms and ill-defined conditions	103	57,201
49	Open wounds of head, neck and trunk	126	56,464
50	Other non-traumatic joint disorders	110	56,064

CCS - Clinical Classification System; COPD - chronic obstructive pulmonary disease; TB - tuberculosis; STD - sexually transmitted disease; HIV - human immunodeficiency virus.
Source: Author's analysis of the most recent SHMI data for the reporting period between February 2018 and January 2019 (NHS Digital, 2018d)

In-hospital mortality

The total number of in-hospital deaths per year was similar each year between 2013 and 2018, with the range between 262,035 and 293,770 in-hospital deaths per year (figure 5.4).

Figure 5.4 Number of in-hospital deaths in the UK NHS between 2013 and 2018



Source: Author's analysis of the SHMI dataset for the years 2013 to 2018 (NHS Digital, 2018d)

The 50 conditions selected based on number of spells where arranged by the number of expected deaths in hospital; from that, 10 conditions were selected. These 10 conditions would be included as candidature conditions and further

analysis and collection of data were limited to these conditions. The expected and observed in-hospital mortality numbers are presented in table 5.3. The highest number of deaths was observed for pneumonia patients, with 42,445 expected in-hospital deaths and 42,415 observed deaths. The lowest observed number of deaths included in further analysis was for patients with gastrointestinal haemorrhage, which was still a large number of 3,790 expected and 3,765 observed in hospital deaths.

Table 5.3 Top 10 CCS diagnostic groups by number of observed and expected deaths in UK NHS trusts for the reporting period between February 2018 and January 2019

Summary description	Diagnosis group number	Sum of expected deaths	Sum of observed deaths
Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	73	42,445	42,415
Septicaemia (except in labour), shock	2	30,775	30,755
Acute cerebrovascular disease	66	15,980	16,020
Congestive heart failure; non-hypertensive	**65**	**10,635**	**10,635**
Chronic obstructive pulmonary disease and bronchiectasis	**75**	**8,380**	**8,405**
Urinary tract infections	101	7,265	7,265
Acute myocardial infarction	57	5,970	5,935
Fracture of neck of femur (hip)	120	5,190	5,160
Acute bronchitis	74	4,840	4,835
Gastrointestinal haemorrhage	96	3,790	3,765

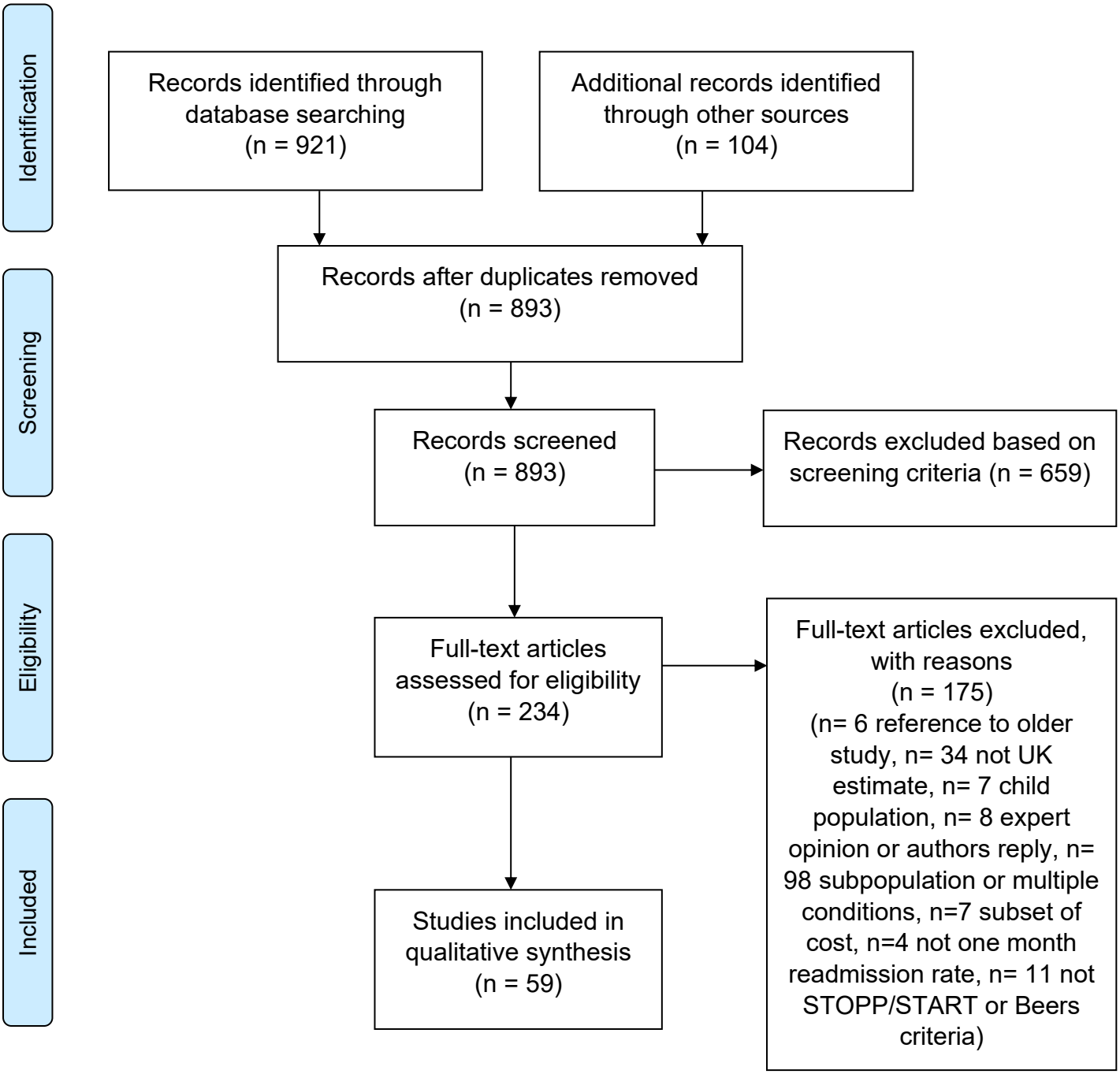
Bold = chronic care conditions
CCS - Clinical Classification System
Source: Author's analysis of the most recent SHMI data for the reporting period between February 2018 and January 2019 (NHS Digital, 2018d)

5.3.2.2 Domain 2: Polypharmacy

For the second domain, apart from estimates of mortality and emergency admissions, data were collected through a literature review. The search was conducted only for 10 conditions, which were selected based on the public health importance described in the first domain. The data were provided for: emergency readmission rates within one month, economic burden and PIP rate.

The initial database search resulted in 921 articles identified. A snowballing of references and search of grey literature identified a further 104 articles. The full text was extracted for 234 articles which were reviewed in full. There were 59 articles that met the inclusion criteria and they were included in the review. The PRISMA diagram (figure 5.5) presents the review process and details reasons for exclusion of the rest of the articles.

Figure 5.5 PRISMA flow diagram for literature review of economic burden, emergency readmission rates and PIP rates of 10 CCS diagnostic groups with biggest public health importance.



PRISMA diagram adapted from (Liberati *et al*., 2009).

Emergency admissions

The data about emergency admissions for 10 conditions come from published analysis of routinely collected hospital administrative data, where a total of 4,317,866 emergency inpatient admissions to all public acute hospitals in England were analysed (Aylin *et al*., 2010). The data show that the highest number of emergency admissions – 106,951 – was observed for COPD patients. The lowest number of emergency admissions – 16,719 – was observed for patients with septicaemia. The numbers of emergency admissions for all 10 conditions are presented in table 5.4.

Emergency readmission rates within one month

There were 17 studies that provided information about emergency readmission rates within one month from the discharge. There were six studies which looked at more than one medical condition. Emergency readmission rates for patients with heart failure ranged from 17.5% to 31.8% (based on six studies); for COPD, 10.2%-28.0% (seven studies); for pneumonia, 11.0%-17.1% (three studies); for septicaemia, 6.7% (one study); for acute cerebrovascular disease, 9.0%-39.3% (four studies); for urinary tract infections, 6.4%-17.1% (two studies); acute myocardial infarction, 9.0%-15.3% (four studies); fracture of hip, 6.0%-12.4% (five studies); acute bronchitis, 1.9% (one study) and for gastrointestinal haemorrhage, 5.0% (one study). All the estimated readmission rates are presented in table 5.5, with references provided for the above figures.

Economic burden

There were 27 articles that looked at economic burden of one of the 10 conditions included in the review (table 5.6). The costs in the review were expressed in UK pounds sterling at a 2017-18 price base, adjusted using the Bank of England inflation calculator and conversion rates from 2018 if necessary. Some of the studies provided more than one estimate of economic burden either based on different prevalence of the disease used for the calculations or the 95% confidence interval used in the costing analysis. There were 11 studies that provided the total economic burden (direct and indirect costs) of the medical condition in the UK and 16 studies that only looked at direct costs.

The average annual economic burden of heart failure ranged between £804 mln – £4,346 mln (based on four studies); COPD was £928 mln – £3,532 mln (four studies); pneumonia was £896 mln (one study); septicaemia was £8,086 mln – £17,020 mln (one study); acute cerebrovascular disease was £1,891 mln – £10,895 mln (two studies); urinary tract infections was £158 mln – £359 mln (two studies); acute myocardial infarction was £133 mln – £552 mln (three studies); fracture of hip was £607 mln – £2,849 mln (seven studies); acute bronchitis was £70 mln (one study); gastrointestinal haemorrhage was £363 mln (one study).

Potentially inappropriate prescribing (PIP) rate

The review identified 15 studies that looked at PIPs for the 10 conditions (table 5.7). The PIP rate for patients with heart failure ranged from 15% to 58% (based on six studies); for COPD, 25%-54% (five studies); for pneumonia, 21%-53% (three studies); for acute cerebrovascular disease, 18%-45% (three studies); for urinary tract infections, 46%-48% (two studies); for acute myocardial infarction, 43%-61% (two studies); for fracture of hip, 49%-90% (eight studies); and for gastrointestinal haemorrhage, 48% (one study). There were no studies identified which looked at prevalence of PIPs for septicaemia or acute bronchitis patients.

Table 5.4 Top 10 CCS diagnostic groups by number of emergency admissions for the reporting period between April 2005 and March 2006

Summary description	Diagnosis group number	Number of emergency admissions	Emergency admissions (% of all emergency admissions) [1]
Chronic obstructive pulmonary disease and bronchiectasis	**75**	**106,951**	**2.48%**
Acute bronchitis	74	103,224	2.39%
Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	73	102,465	2.37%
Urinary tract infections	101	92,721	2.15%
Acute cerebrovascular disease	66	70,500	1.63%
Acute myocardial infarction	57	68,932	1.60%
Gastrointestinal haemorrhage	96	57,937	1.34%
Congestive heart failure; non-hypertensive	**65**	**56,394**	**1.31%**
Fracture of neck of femur (hip)	120	53,153	1.23%
Septicaemia (except in labour), shock	2	16,719	0.39%

Bold = chronic care conditions
CCS - Clinical Classification System

Table 5.5 Emergency readmission rates within one month from discharge, for the 10 CCS diagnostic groups with the biggest public health importance

Study	Year	Emergency readmission rate within one month* (%)	Sample size
Congestive heart failure; non-hypertensive			
(Friebel, Hauck, Aylin & Steventon, 2018)	2015-2016	17.8%	38,349
(Friebel *et al*., 2018)	2006-2007	17.5%	32,051
(Bottle, Honeyford, Chowdhury, Bell & Aylin, 2018)	2009-2011	19.8%	77,801
(Davison *et al*., 2016)	2007-2009	20.1%	1,849
(Bottle, Goudie, Cowie, Bell & Aylin, 2015)	2009-2012	19.1%	105,441
(Bottle *et al*., 2014)	2008-2010	18.0%	84,212
(Demir, Chaussalet, Xie & Millard, 2008)	2003	21.2%	70,280
(Demir *et al*., 2008)	2002	21.0%	72,469
(Demir *et al*., 2008)	2001	21.4%	74,823
(Demir *et al*., 2008)	2000	23.4%	77,790

(Demir *et al*., 2008)	1999	27.6%	81,907
(Demir *et al*., 2008)	1998	31.8%	81,954
COPD and bronchiectasis			
(Morton *et al*., 2019)	2013-2015	13.0%	19,097
(Friebel *et al*., 2018)	2015-2016	16.9%	103,871
(Friebel *et al*., 2018)	2006-2007	16.5%	97,306
(Hekkert *et al*., 2018)	2014	24.3%	112,078
(Bottle, Honeyford, *et al*., 2018)	2009-2011	16.5%	96,053
(Harries *et al*., 2017)	2006-2010	10.2%	20,932
(Steer, Norman, Afolabi, Gibson & Bourke, 2012)	2008-2010	19.1%	920
(Demir *et al*., 2008)	2003	22.0%	112,918
(Demir *et al*., 2008)	2002	22.2%	101,970
(Demir *et al*., 2008)	2001	22.3%	99,795
(Demir *et al*., 2008)	2000	23.1%	98,470
(Demir *et al*., 2008)	1999	24.2%	101,819
(Demir *et al*., 2008)	1998	28.0%	96,841

Pneumonia (excluding TB/STD)			
(Friebel *et al*., 2018)	2015-2016	15.8%	106,554
(Friebel *et al*., 2018)	2006-2007	13.7%	46,224
(Hekkert *et al*., 2018)	2014	17.1%	172,281
(Sg2 Service Kit, 2011)	2009-2010	11.0%	–**
Septicaemia (except in labour), shock			
(Inada-Kim, Page, Maqsood & Vincent, 2017)	2013-2014	6.7%	47,475
Acute cerebrovascular disease			
(Friebel *et al*., 2018)	2015-2016	10.5%	45,601
(Friebel *et al*., 2018)	2006-2007	9.9%	34,835
(Palmer, Bottle, Davie, Vincent & Aylin, 2013)	2009-2010	11.0%	91,936
(Sg2 Service Kit, 2011)	2009-2010	9.0%	–**
(Demir *et al*., 2008)	2003	26.2%	92,120
(Demir *et al*., 2008)	2002	29.0%	94,815
(Demir *et al*., 2008)	2001	28.3%	90,579
(Demir *et al*., 2008)	2000	29.3%	89,774

(Demir *et al*., 2008)	1999	35.3%	92,653
(Demir *et al*., 2008)	1998	39.3%	90,826
Urinary tract infections			
(Inada-Kim *et al*., 2017)	2013-2014	6.4%	7,088
(Hekkert *et al*., 2018)	2014	17.1%	156,526
Acute myocardial infarction			
(Friebel *et al*., 2018)	2015-2016	15.3%	39,037
(Friebel *et al*., 2018)	2006-2007	15.1%	43,416
(Hekkert *et al*., 2018)	2014	12.2%	75,361
(Kwok *et al*., 2017)	2017	9.0%	1,869
Fracture of neck of femur (hip)			
(Friebel *et al*., 2018)	2015-2016	7.1%	64,155
(Friebel *et al*., 2018)	2006-2007	7.6%	59,267
(Hekkert *et al*., 2018)	2014	10.6%	66,368
(Laudicella, Li Donni & Smith, 2013)	2008	11.6%	290,000***
(Laudicella *et al*., 2013)	2007	12.4%	290,000***

(Laudicella *et al*., 2013)	2006	12.4%	290,000***
(Laudicella *et al*., 2013)	2005	12.3%	290,000***
(Laudicella *et al*., 2013)	2004	11.4%	290,000***
(Laudicella *et al*., 2013)	2003	10.5%	290,000***
(Khan, Hossain, Dashti & Muthukumar, 2012)	2009-2010	11.8%	467
(Sg2 Service Kit, 2011)	2009-2010	6.0%	–**
Acute bronchitis			
(Inada-Kim *et al*., 2017)	2013-2014	1.9%	52
Gastrointestinal haemorrhage			
(Oakland *et al*., 2015)	2015	5.0%	2,284

* Depending on the study, 28 days or 30 days;
** Study included 661,893 patient records, with multiple medical conditions covered. Information on number of patients by disease group was not available;
*** Number of patients for the whole study, data disaggregated by each year were not available.
CCS - Clinical Classification System; COPD - chronic obstructive pulmonary disease; TB - tuberculosis; STD - sexually transmitted disease.

Table 5.6 Economic burden defined as direct or indirect cost of disease (or the combination of two), for 10 CCS diagnostic groups with the biggest public health importance

Study	Year	Direct cost (£ million/year)	Indirect cost (£ million/year)	Total (£ million/year)
Congestive heart failure; non-hypertensive				
(Cook, Cole, Asaria, Jabbour & Francis, 2014)	2012	2,990.44*	1,356.02*	4,346.46*
(Sutherland, 2010)	2008	819.17	–	–
(Stewart *et al*., 2002)	1995	1,352.10	–	–
(McMurray, Hart & Rhodes, 1993)	1990-1991	803.79	–	–
COPD and bronchiectasis				
(Trueman, Woodcock & Hancock, 2017)	2014	2,031.33	67.09	2,098.42
(McLean *et al*., 2016)	2011	1,795.90	–	–
(McLean *et al*., 2016) Low estimate**	2011	1,412.70	–	–
(McLean *et al*., 2016) High estimate**	2011	2,993.10	–	–

(NHS Medical Directorate, 2012)	2012	927.99	–	–
(Britton, 2003) High estimate***	2000-2001	1,767.42	1,764.58	3,532.00
(Britton, 2003) Low estimate***	2000-2001	813.16	811.87	1.625.03
Pneumonia (excluding TB/STD)				
(Guest & Morris, 1997)	1992	895.92	–	–
Septicaemia (except in labour), shock				
(Hex, Retzler, Bartlett & Arber, 2017) Estimate 1^	2015	902.53	7,548.12	8,450.64
(Hex *et al*., 2017) Estimate 1^ (Low estimate)**	2015	677.12	7,408.48	8,085.59
(Hex *et al*., 2017) Estimate 1^ (High estimate)**	2015	1,233.97	9,879.18	11,113.15
(Hex *et al*., 2017) Estimate 2^	2015	1,610.17	10,639.62	12,250.09
(Hex *et al*., 2017)	2015	1,214.91	10,392.65	11,607.56

Estimate 2^ (Low estimate)**				
(Hex *et al*., 2017) Estimate 2^ (High estimate)**	2015	2,147.32	14,872,77	17,020.09
Acute cerebrovascular disease				
(Xu *et al*., 2018)	2015-2016	1,890.91	–	–
(BHF, 2017)	2015	4,440.99††	1,325.89††	5,766.88††
(Saka, McGuire & Wolfe, 2005)	2003-2004	4,401.73	6,493.34	10,895.07
Urinary tract infections				
(Smith *et al*., 2019)	2017	56.32	216.39	272.71
(Smith *et al*., 2019) Low estimate**	2017	38.55	98.90	137.44
(Smith *et al*., 2019) High estimate**	2017	80.40	279.02	359.41
(Plowman *et al*., 2001)	1994-1995	242.07	–	–
(Plowman *et al*., 2001) Low estimate**	1994-1995	158.19	–	–
(Plowman *et al*., 2001) High estimate**	1994-1995	325.97	–	–

Acute myocardial infarction				
(Gaughan, Mason, Street & Ward, 2012) Estimate 1†	2007-2008	218.99	–	–
(Gaughan *et al*., 2012) Estimate 2†	2007-2008	132.97	–	–
(Häkkinen, Chiarello, Cots, Peltola & Rättö, 2012) Estimate 1†	2007-2008	257.33	–	–
(Häkkinen *et al*., 2012) Estimate 2†	2007-2008	156.24	–	–
(Tiemann, 2008) Estimate 1†	2005	551.6^^^	–	–
(Tiemann, 2008) Estimate 2†	2005	334.93^^^	–	–
Fracture of neck of femur (hip)				
(Judge *et al*., 2016)	2013	1,367.81	–	–
(Leal *et al*., 2016)	2012-2013	1,310.78	–	–
(Marsh *et al*., 2007)	2007	–	–	2,730.00

(Lawrence, White, Wenn & Moran, 2005)	2003	1,133.79	1,351.21	2,485.00
(Finnern & Sykes, 2003)	2001	879.34^^	–	–
(Burge, Worley, Johansen, Bhattacharyya & Bose, 2001)	2000	–	–	2,849.42
(Hollingworth, Todd & Parker, 1996)	1991-1992	607.39	–	–
Acute bronchitis				
(McGuire *et al*., 2001)	1994-1995	69.76	–	–
Gastrointestinal haemorrhage				
(Campbell *et al*., 2015)	2012-2013	180.30	182.93	363.23

* Originally reported in USD, at a price base of 2012. The cost was converted using the exchange rate from January 2018; 1 USD = 0.7364 GBP and adjusted for inflation.
** Low and high estimates based on 95% confidence intervals.
*** Based on estimated prevalence of patients with COPD; high estimate 1.3 million people; low estimate 600,000 people.
^ Estimate 1 was based on estimated incidence of 147,000 per year; estimate 2 was based on incidence of 260,000 per year.
^^ Originally reported in EUR, at a price base of 2001. The cost was converted using the exchange rate from January 2018; 1 EUR = 0.8870 GBP and adjusted for inflation.
^^^ Originally reported in EUR, at a price base of 2005. The cost was converted using the exchange rate from January 2018; 1 EUR = 0.8870 GBP and adjusted for inflation.
† Only cost of hospitalisation included. Estimate 1 is based on population of 85,240 inpatients (Gaughan *et al*., 2012). Estimate 2 is based on 51,755 inpatients (Pearson-Stuttard *et al*., 2012).
†† Originally reported in EUR, at a price base of 2015. The cost was converted using the exchange rate from January 2018; 1 EUR = 0.8870 GBP and adjusted for inflation.
CCS – Clinical Classification System; COPD – chronic obstructive pulmonary disease; TB – tuberculosis; STD – sexually transmitted disease

Table 5.7 Potentially inappropriate prescribing (PIP) rate for the 10 CCS diagnostic groups with the biggest public health importance

Study	Year	PIP rate (%)	Tool used for measuring the PIP rate	Sample size
Congestive heart failure; non-hypertensive				
(Komagamine, 2018)	2014-2016	49%	Beers criteria	153
(Vezmar Kovačević *et al*., 2014)	2012	15%	STOPP/START criteria	230
(Bermingham *et al*., 2014)	2009-2011	58%	STOPP/START criteria	350
(Bradley *et al*., 2014)	2007	30%	STOPP/START criteria	11,329
(Wawruch *et al*., 2008)	2003-2005	28%	Modified Beers criteria	205
(Rothberg *et al*., 2008)	2002-2005	52%	Modified Beers criteria	109,071
COPD and bronchiectasis				
(Komagamine, 2018)	2014-2016	54%	Beers criteria	57
(Wawruch *et al*., 2008)	2003-2005	25%	Modified Beers criteria	119
(Rothberg *et al*., 2008)	2002-2005	42%	Modified Beers criteria	44,582
(Vezmar Kovačević *et al*., 2014)	2012	54%	STOPP/START criteria	94

(Bradley *et al*., 2014)	2007	53%	STOPP/START criteria	34,547
Pneumonia (excluding TB/STD)				
(Komagamine, 2018)	2014-2016	53%	Beers criteria	141
(Lee *et al*., 2013)	2012	21%	STOPP/START criteria	117
(Rothberg *et al*., 2008)	2002-2005	46%	Modified Beers criteria	122,732
Acute cerebrovascular disease				
(Komagamine, 2018)	2014-2016	40%	Beers criteria	108
(Wawruch *et al*., 2008)	2003-2005	18%	Modified Beers criteria	139
(Rothberg *et al*., 2008)	2002-2005	45%	Modified Beers criteria	57,204
Urinary tract infections				
(Komagamine, 2018)	2014-2016	48%	Beers criteria	58
(Rothberg *et al*., 2008)	2002-2005	46%	Modified Beers criteria	39,397
Acute myocardial infarction				
(Vezmar Kovačević *et al*., 2014)	2012	43%	STOPP/START criteria	72
(Rothberg *et al*., 2008)	2002-2005	61%	Modified Beers criteria	70,581

Fracture of neck of femur (hip)				
(Gleich *et al*., 2019)	2016	49%	STOPP/START criteria	95
(Komagamine & Hagane, 2017)	2015	65%	Beers criteria	158
(Iaboni, Rawson, Burkett, Lenze & Flint, 2017)	2008-2012	51%	Beers criteria	477
(Lönnbro & Wallerstedt, 2017)	2009	85%	STOPP/START criteria	200
(Ekstam Kragh, 2017)	2006	81%	Beers criteria	2,043
(Belfrage, Koldestam, Sjöberg & Wallerstedt, 2015)	2009	71%	STOPP/START criteria	200
(Belfrage, Koldestam, Sjöberg & Wallerstedt, 2014)	2009	85%	STOPP/START criteria	200
(Gosch, Wörtz, *et al*., 2014)	2000-2004	90%	STOPP/START criteria	457
Gastrointestinal haemorrhage				
(Komagamine, 2018)	2014-2016	48%	Beers criteria	71

CCS – Clinical Classification System; COPD – chronic obstructive pulmonary disease; TB – tuberculosis; STD – sexually transmitted disease; PIP – potentially inappropriate prescribing.

Summary of all five criteria associated with problematic polypharmacy

Table 5.8 provides a summary of all the data for the five criteria reflecting on problematic polypharmacy. The condition with the highest in-hospital mortality rate was pneumonia, with 14.77% of all in-hospital deaths. The highest emergency admission rates of 2.48% were present for COPD patients. The condition with the highest mean readmission rate within one month of discharge was congestive heart failure (HF). The readmission rate for HF patients ranged from 17.5% to 31.8%. The highest economic burden was observed for septicaemia – between £8,086 million and £17,020 million per annum, however there were big disparities in the methodology used to evaluate the economic burden for different medical conditions. Finally, the highest prevalence of potentially inappropriate prescribing (PIP) ranged between 49% and 90% and was observed for patients with fracture of the hip. In the analysis there were two conditions that can be described as chronic care conditions: HF and COPD.

Table 5.8 Summary of the five criteria associated with problematic polypharmacy for the 10 CCS diagnostic groups with the biggest public health importance

Summary description	Diagnosis group number	In-hospital mortality (% of all in-hospital mortality) [1]	Emergency admissions (% of all emergency admissions) [2]	Readmission rate within one month (%) [3]	Economic burden (£million/year) [3]	PIP rate (% of the population) [3]
Congestive heart failure; non-hypertensive	**65**	**3.62%**	**1.31%**	**17.5%-31.8%**	**804-4,346**	**15%-58%**
COPD and bronchiectasis	**75**	**2.95%**	**2.48%**	**10.2%-28.0%**	**928-3,532**	**25%-54%**

Pneumonia (excluding TB/STD)	73	14.77%	2.37%	11.0%-17.1%	896	21%-53%
Septicaemia (except in labour), shock	2	11.99%	0.39%	6.7%	8,086-17,020	–
Acute cerebrovascular disease	66	5.55%	1.63%	9.0%-39.3%	1,891-10,895	18%-45%
Urinary tract infections	101	2.41%	2.15%	6.4%-17.1%	158-359	46%-48%
Acute myocardial infarction	57	2.05%	1.60%	9.0%-15.3%	133-552	43%-61%
Fracture of neck of femur (hip)	120	1.86%	1.23%	6.0%-12.4%	607-2,849	49%-90%
Acute bronchitis	74	1.70%	2.39%	1.9%	70	–
Gastrointestinal haemorrhage	96	1.29%	1.34%	5.0%	363	48%

CCS – Clinical Classification System; COPD – chronic obstructive pulmonary disease; TB – tuberculosis; STD – sexually transmitted disease; PIP – potentially inappropriate prescribing.
Bold = chronic care conditions.
[1] (NHS Digital, 2018d)
[2] (Aylin *et al*., 2010)
[3] Results based on ranges from literature review described in section 5.3.2.2 ‘Domain 2: Polypharmacy’ of this chapter

5.3.2.3 Domains 3 and 4: Chronic care conditions and age

Out of the analysed conditions, two conditions – congestive heart failure and COPD – could be classified as chronic care conditions that are associated with problematic polypharmacy. These two conditions also meet the age criteria, because they are more common in older age groups. Heart failure usually affects older patients, with an average age at presentation of 77 years in the UK (Conrad *et al*., 2018). The average age at admission for COPD patients is 73 years (Stone *et al*., 2018). As previously described, COPD and HF are amongst the top 50 medical conditions for all-cause admission to hospital (NHS Digital, 2018d) and the top 15 for emergency admissions (Aylin *et al*., 2010). From the 10 analysed medical conditions COPD and HF had on average the highest readmission rates.

Therefore, older patients with these two conditions were selected as the best candidates for inclusion in the long-term cost-utility analysis of comprehensive medication review. The timeframe of the PhD does not allow for completion of cost-utility analysis for both conditions, so the next section will present a description of both conditions and justification of the final decision of which single medical condition will be included in the cost-utility analysis.

5.3.3 Stage 3: The final choice of one target population based on the four-domain model

Data presented show that both HF and COPD are chronic conditions which have recognised morbidity and mortality and are a common reason for admission and readmission to hospital. Having chronic conditions, this group of patients is at risk of polypharmacy and these conditions are often associated with comorbidities. Patients receiving treatment for multiple conditions and polypharmacy experience more PIPs, which the CMR tries to address. These are also conditions that cause high financial pressure on the NHS, due to their high levels of NHS hospital resources use. The conditions are also some of the leading causes of in-hospital mortality. As such, they represent good candidate conditions for the evaluation of the potential economic impact of polypharmacy and CMR.

In this section, I will describe the reasoning behind the choice of the final medical condition as the target population to be included in the cost-utility analysis. First, I will describe the two conditions by providing their definitions and discussing the

epidemiology, classification of the disease and the symptoms. I will also provide information about the diagnosis, treatment, management and prognosis for the two conditions. Providing this information aims to present the clinical context associated with the two candidate conditions and facilitates the choice between them. Finally, I will describe which condition has been chosen for the long-term analysis of the cost-utility of CMR and provide as to arguments why this choice was made.

5.3.3.1 Congestive heart failure

Definition of HF

According to the European Society of Cardiology, heart failure (HF) is “a clinical syndrome characterised by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress” (European Society of Cardiology, 2016).

Epidemiology of HF

In developed countries, the prevalence of heart failure is around 1-2% of adults, increasing with age. It affects up to 10% of the population by age 70 (European Society of Cardiology, 2016). Estimates based on CPRD data of four million people in the UK suggest that in 2014 there were 920,616 cases of heart failure (1.8% of the adult population). The incidence of heart failure in the UK decreased by 7% between 2002 and 2014, but because the population size and age have increased, the absolute number of newly diagnosed heart failure cases increased by 12% and the absolute number of prevalent heart failure cases increased by 23% (Conrad *et al*., 2018). Moreover, there are many people in the UK who have unrecognised heart failure; it is estimated that one in six patients over 65 years old who present to primary care with breathlessness on exertion has unrecognised heart failure (European Society of Cardiology, 2016). Because of underdiagnosed heart failure, the economic and health impact of the medical condition can be underestimated. As mentioned before, the average age for presentation of a patient with heart failure is 77 years. Heart failure patients often have recognised comorbidities such as

hypertension or diabetes and on average a heart failure patient has 5.4 (SD 2.5) comorbidities (Conrad *et al*., 2018), with the associated risk of polypharmacy.

Diagnosis of HF

The diagnosis of HF relies on clinical judgement that considers factors such as the patient's clinical history (e.g. whether the patient had a history of coronary artery disease, hypertension or diuretic use), physical examination (e.g. increased jugular venous pressure, bilateral oedema, displaced apical beat) and clinical investigation. If through clinical judgment the patient is found to be at risk of heart failure, the plasma concentration of natriuretic peptides (NPs) should be measured to identify whether there is a need for echocardiography (European Society of Cardiology, 2016; NICE, 2018a).

Treatment and management of HF

The treatment of heart failure is similar irrespective of the cause. It includes diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and mineralocorticoid receptor antagonist (MRA). Other drugs include a combination of ARB (valsartan) and neprilysin inhibitor (sacubitril), ivabradine, hydralazine and nitrate and digoxin. As such, many heart failure patients are often taking a minimum of three medications before any consideration of comorbidity (European Society of Cardiology, 2016; NICE, 2018a).

Symptoms of HF

HF in most patients is a chronic condition as the changes in the heart muscle pump function are commonly not reversible. However, patients can present with progressive symptoms or with acute or chronic problems.

When patients present acutely, the most common symptom is acute breathlessness or they can present with increasing oedema (swelling) or reduced activities.

Based on the severity of the symptoms and limitations in functioning, HF patients can be classified into four classes based on measures developed by the New York Heart Association (NYHA) in their guideline. Table 5.9 presents the four classes and describes the symptoms which patients experience in each class.

Table 5.9 New York Heart Association functional classification based on severity of symptoms and physical activity

NYHA class	Description of symptoms
NYHA I	The disease does not result in limitation of physical activity. Normal physical activity does not result in undue fatigue, breathlessness or palpitations.
NYHA II	The disease causes slight limitation in physical activity. Patients at rest are usually comfortable, but normal physical activity may result in undue fatigue, breathlessness or palpitations.
NYHA III	Patients experience marked limitation to physical activity. They are comfortable at rest, but even less than normal physical activity results in undue fatigue, breathlessness or palpitations.
NYHA IV	Inability to carry physical activity without discomfort. The patient at rest can experience symptoms of heart failure or the anginal syndrome. If physical activity is undertaken, the discomfort increases.

NYHA, New York Heart Association. Source: (Dolgin, 1994).

Prognosis for HF

The analysis of the SHMI database presented in the results section suggests that HF is one of the leading causes of in-hospital mortality. Out of the analysed medical conditions it was the third most common cause of in-hospital mortality. In recent years, the survival rates for UK NHS heart failure patients have improved, but the prognosis is still poor.

- Based on the most recent primary care CPRD data (from 2016, 2012 and 2007 respectively) out of 55,959 HF patients, 80.8% survived one year. In 2007, the five-year survival rate was 48.2% and 10-year survival rate 26.2% (Taylor *et al*., 2019).
- Another study used the HES administrative database to look at records from 234,719 hospitalised patients. In the mean follow-up time of 1.6 years 130,916 deaths occurred, which was 55.8% of the studied population (Bottle, Ventura, *et al*., 2018).

- The data published in the National Heart Failure Audit report show that in-hospital mortality for patients with heart failure was 9.4% for the period from April 2016 to March 2017 (NCAP, 2018).

5.3.3.2 Chronic obstructive pulmonary disease (COPD)

Definitions of COPD

According to the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (COPD), COPD is: “characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” (GOLD, 2018).

Epidemiology of COPD

Estimates of prevalence of COPD in the general population vary depending on the methodology used in different studies. Because COPD is underdiagnosed, studies based on routinely collected data usually underestimate the real prevalence of COPD in the population, with most such studies providing an estimate of less than 6% of the adult population (GOLD, 2018).

The Burden of Obstructive Lung Diseases (BOLD) program evaluated the prevalence of COPD in 29 countries by conducting a survey using a standardised methodology. BOLD estimated that the global prevalence of COPD was 11.7% (95% CI; 8.4%-15.0%) in 2010. The BOLD program estimated that men are more likely to experience COPD with a prevalence of 11.8% (SE 7.9) for men, and 8.5% (SE 5.8) for women (GOLD, 2018).

In the UK, NICE estimates that there are 1.2 million people (2% of the adult population) diagnosed with COPD and there are 115,000 new diagnoses each year (NICE, 2018b). These figures however do not reflect the whole heath burden as there are many undiagnosed patients. The average age for COPD patients is 73 years; it is present in 9% of people over 70 years of age (Snell *et al*., 2016; Stone *et al*., 2018).

Diagnosis of COPD

COPD can be diagnosed using spirometry. The diagnosis depends on the presence of irreversible airflow obstruction. The diagnosis of COPD should be considered for patients with cough, breathlessness or chronic sputum production. The main risk factors for COPD are tobacco use and exposure to dust, chemicals or fumes at work (Hopkinson, Molyneux, Pink & Harrisingh, 2019).

Treatment and management of COPD

COPD is a chronic care condition and, as with HF, the changes made are irreversible and there is no cure; instead, COPD should be managed to avoid exacerbations. The most common first intervention with patients with COPD is smoking cessation interventions. COPD can also be managed by inhalers: beta-2 agonist inhalers or antimuscarinic inhalers and steroid inhalers. The medicines used in COPD patients include theophylline, mucolytic, steroids and antibiotics. Patients with COPD can also be referred to specialist pulmonary rehabilitation programmes and in the worst cases have surgery or a lung transplant (NICE, 2018b).

Symptoms of COPD

Common symptoms of COPD are: chronic cough, breathlessness, regular sputum production and winter ‘bronchitis’ wheeze. COPD patients can also experience fatigue, weight loss, reduced tolerance for exercise, cough with blood, ankle swelling and chest pain (NICE, 2018b).

Prognosis for COPD

NICE estimates that in the UK, the age-standardised mortality rate is 210.7 deaths per million people between 2001 and 2010 (NICE, 2018a). The analysis of the SHMI database suggests that from the ten analysed conditions, COPD was the fifth most common reason for in-hospital mortality, with 2.95% of all recorded in-hospital deaths resulting from COPD (NHS Digital, 2018d). It is estimated that around 30,000 people in the UK die each year from COPD (Snell *et al*., 2016). A study that looked at 6,261 patients with COPD with a mean follow-up of eight years has established that for 65-year-olds the reduction in life expectancy was between 0.3 and 5.8 years (depending on the severity of disease and smoking status) (Shavelle, Paculdo, Kush,

Mannino & Strauss, 2009). In UK patients the five-year survival rate for the most severe type of COPD is as low as 24%-30% (Seamark, Seamark & Halpin, 2007).

5.3.3.3 Target population included in long-term cost-utility analysis of CMR

Both HF and COPD are appropriate candidate conditions that could be used for long-term cost-utility analysis of CMR in the hospital setting. Due to the time constrain of this PhD it was only possible to look at one of these conditions. I selected HF as the target population, because although the total number of emergency admissions for patients with HF is lower than for COPD, the published readmission rates suggest higher one-month readmission for patients with HF. The in-hospital mortality is slightly higher for patients with HF compared to COPD patients and the economic burden is bigger. The data about the prevalence of PIPs amongst HF and COPD patients were inconclusive. Therefore, three out of five criteria for problematic polypharmacy favoured the choice of HF as the target population. It has to be mentioned that the choice of COPD as the target population would be equally valid.

5.4 Discussion

This chapter identified patients with heart failure as the target population of patients who are subject to problematic polypharmacy and who can benefit from CMR. Heart failure, by being a chronic care condition that has high public health importance and significant use of UK NHS hospital resources, fits well with the criteria for selecting a target population provided by NICE in their Medicines Optimisation guidelines (NICE, 2015a). Conducting a cost-utility analysis for a high-cost and high-disease burden population, where CMR would probably generate the most value for money, also fits well with the health economics principles of efficient allocation of scarce resources.

5.4.1 Contribution to the field

The broad scope of the CMR intervention makes it complex for targeting appropriate patients to deliver the best care. In an ideal world, everybody would be able to receive the best quality comprehensive medication review, however in a scarce-resource setting such as healthcare it is important to ensure that all patients with the greatest need receive the intervention.

To my knowledge, this is the first attempt at identifying a target population for cost-utility analysis of CMR. Therefore, I will discuss the results in relation to the guidelines that describe who can benefit from CMR.

Target population in guidelines on CMR

The current literature about medicines optimisation is limited in terms of choosing the correct population of patients who would most benefit from CMR. In section 5.1 'Background', I describe what the current guidelines say about the target population for CMR. The guidelines by NICE, King's Fund and SGPMCG describe the target population in a very broad way, which could be summarised as: older patients who are subject to polypharmacy. The population from guidelines truly reflect all the patients that could need their medicines optimised, however in terms of cost-utility analysis this population is too wide and too diverse to complete a sophisticated cost-utility model. In chapter 4, I described an attempt to evaluate the cost-effectiveness of CMR for all older patients on polypharmacy. The results were promising, but due to the broad target population included in the model the study had methodological limitations (e.g. could be conducted for only a 12-month time-horizon). Therefore, the study needed the results to be confirmed by narrowing down the target population to do a long-term cost-utility analysis. Results from this chapter reflect well the principles mentioned in NICE guidelines on Medicines Optimisation and by choosing a set of criteria that reflect the characteristics of the population from the guidelines it was possible to narrow down the target population to a single medical condition which was appropriate to include in the long-term analysis.

5.4.2 Contribution to thesis and implication for further research

This study provided a significant contribution to the overall thesis by answering one of the research questions:

What are the target populations of patients acutely admitted to hospital who could benefit from CMR? Out of those, which population should be included in the modelling of long-term cost-effectiveness of CMR?

The first part of the research question is answered by extensive literature search and description of all the patient groups who could benefit from CMR. Subsequent analysis based on criteria for problematic polypharmacy and public health importance allows us to determine the ten candidate populations to be included in the long-term cost-utility model. Finally, section 5.3.3 of this chapter selects patients with heart failure as the target population.

Results from this chapter allow the PhD to be focused on two perspectives:

1. Modelling the cost-effectiveness of CMR for a whole diverse group of patients, but over a short period of time (12-month time horizon). This is described in chapter 4 of the thesis.
2. Modelling cost-utility of CMR for a much more defined target population, which allows a more in-depth modelling approach over a long-term period (life-time horizon). This is described in chapter 6 of the thesis.

This chapter has provided evidence about target populations for CMR intervention, which can be used in further exploration of the cost-effectiveness of CMR. Future research can focus on analysing the cost-effectiveness of CMR for all identified populations. The natural next step in researching the topic would be to conduct a cost-effectiveness analysis of CMR for the COPD population. COPD is a chronic care condition, accountable for 2.95% of all in-hospital mortality (NHS Digital, 2018d). It has a high emergency admission rate of 2.48% of all emergency admissions (Aylin *et al*., 2010) and an even higher emergency readmission rate that ranges from 10.2% to 28.0% (Bottle, Honeyford, *et al*., 2018; Demir *et al*., 2008; Friebel *et al*., 2018; Harries *et al*., 2017; Hekkert *et al*., 2018; Morton *et al*., 2019; Steer *et al*., 2012). COPD also costs the UK NHS between £928 million and £3,532 million per year (Britton, 2003; McLean *et al*., 2016; NHS Medical Directorate, 2012; Trueman *et al*., 2017). What is even more disturbing is the fact that a large study of 1,019,491 patient records in CPRD data found that more than half 18,156 of 34,547 COPD patients (52.6%) received at least one PIP, measured by the STOPP/START criteria (Bradley *et al*., 2014). In other studies, the rate of PIPs for COPD patients ranged from 25% to 54% (Komagamine, 2018; Rothberg *et al*., 2008; Vezmar Kovačević *et al*., 2014; Wawruch *et al*., 2008).

The focus of the PhD is patients with heart failure, and the analysis of COPD was out of scope of the PhD. However, evidence from the PhD provides a strong recommendation that future research should focus on conducting a cost-effectiveness analysis of CMR for COPD patients.

The other approach would be to focus research efforts to find populations and settings where CMR is no longer cost-effective. Finding the crossing point at which CMR stops being cost-effective could enable us to determine the factors that influence value for money of CMR and why it is cost-effective in one area but not the other.

5.4.3 Strengths and limitations

This is the first attempt to establish the target population of patients who could benefit from CMR for conducting a complex cost-effectiveness analysis of the CMR intervention. The study can contribute to current knowledge about the cost-effectiveness of CMR by providing a possible candidate target population for evaluation. The focus of this PhD was on one of the target populations identified in this study, but the strength of this study is that it provides other target populations that future research should consider, most notably cost-effectiveness analysis of CMR for patients with COPD.

The strength of this study is that it reflects the current health needs of the population. The criteria selected to determine the target population reflect public health importance with data about morbidity and mortality, data about hospital utilisation (emergency admission and readmission to hospital) and the cost of disease all reflected in the analysis. Finally, the analysis includes data about potentially inappropriate prescribing, which is a crucial factor for determining a target population of patients for cost-utility analysis of CMR.

The target population was chosen to reflect the public health importance of the disease, but also to reflect the patients that would benefit most from CMR. Therefore, the criteria are closely related to the guidelines of NICE medicines optimisation (NICE, 2015a) so that they are based on the current best available evidence and current medical standards in the UK NHS.

The evidence for in-hospital mortality and the admission data come from routinely collected data in the form of Summary Hospital-level Mortality Indicator (SHMI). The SHMI is based on HES data, which holds records for all the NHS trusts in the UK. The data in this chapter also come from a comprehensive literature search of the most recent evidence about potentially inappropriate prescribing, economic burden of the disease and readmission rates.

The limitations of this study include the fact that the analysis does not provide information about subpopulations of patients with HF that could be included in the cost-utility analysis of CMR. Even though this study did not provide information on possible subgroup analysis for health economic modelling, chapter 3 was able to provide that information. In chapter 6, subgroup analysis was conducted based on chapter 3 (the in-depth analysis of CMR intervention), based on the age of patients and based on literature about heart failure patients.

Patients who could benefit from CMR are patients with multiple medical conditions, however the criteria selected in this chapter did not allow for reflection of the findings about comorbidities. This limitation was addressed in the cost-utility analysis of CMR in chapter 6. The main inclusion criterion for the cost-utility analysis was to include patients with heart failure, but this did not limit the number of comorbidities the patients may have. Data in chapter 6 come from HES data and include all patients diagnosed with HF, including those with multiple medical conditions. This is also reflected in the type of drugs that were included in the analysis e.g. benzodiazepines and neuroleptics to account for patients with mental health conditions or medicines that treat physical conditions such as proton pump inhibitors for peptic ulcers or NSAIDs for relieving pain that can be used in a whole spectrum of diseases.

Finally, there is limitation of the large heterogeneity between the studies included in the literature review. This produces large ranges of costs, readmission rates and PIPs for some of the conditions. Unfortunately, this also prevented the results being summarised using meta-analysis.

5.5 Conclusions

This chapter highlighted the considerable body of research about emergency admissions, in-hospital mortality, economic burden, readmissions and potentially

inappropriate prescribing for 10 medical conditions included in the analysis. In the end, the choice of medical conditions to be included as a target population for the long-term cost-utility analysis of CMR was made between two medical conditions: heart failure and COPD. Both conditions filled the criteria set in the four-domain model and were characterised by high rates for all key measures. The final choice was to include heart failure as a target population for the analysis, with COPD highlighted as a recommended priority for future research.

CHAPTER 6 LONG-TERM COST-EFFECTIVENESS OF COMPREHENSIVE MEDICATION REVIEW

The main purpose of this chapter is to answer research question number 5:

Is CMR a cost-effective intervention over a long-term (lifetime) time horizon, compared with usual care for the identified target population, from the perspective of the UK NHS and PSS?

In chapter 4, I described the cost-effectiveness of CMR for patients aged 65 years or older over a 12-month time horizon. The conclusion was that CMR has the potential to be a cost-saving intervention and that it would be useful to explore the long-term cost-effectiveness of CMR by estimating the potential health gain measured in quality-adjusted life years (QALY). To allow this more in-depth cost-utility modelling it was necessary to focus on a target population.

Chapter 5 describes the approach to defining a target population by narrowing down the study group: older patients with chronic healthcare conditions that are known to be of significant public/population health importance (high morbidity and mortality) with high treatment costs and at risk of problematic polypharmacy. After analysis of 142 medical conditions, heart failure was chosen as the target patient population for the analysis as it meets the requirements outlined above.

Chapter 6 draws upon chapters 4 and 5 to present the findings of a long-term cost-utility analysis of CMR by comparing it with usual care in hospitalised patients with chronic heart failure (HF) with an acute hospital admission, from the perspective of the UK NHS and personal social services (PSS).

This chapter is structured as follows:

Section 6.1 describes the decision problem with the focus on the PICO (Population, Intervention, Comparator, Outcome) of the analysis. The target population of patients with HF is presented, with additional information about subpopulations that will be studied within the analysis. The intervention described is CMR undertaken using the STOPP/START criteria, a tool for determining the quality of prescribing. CMR is compared against usual care in patients with heart failure. The outcomes described

in the analysis are: intermediate benefit outcomes (reduction in potentially inappropriate prescribing (PIP)), final health benefit outcome measured in quality-adjusted life years (QALYs) and cost outcomes (the cost of medicines and cost of treatment for ADE of PIPs). This section presents the most common PIPs in hospitalised patients with heart failure and in the general population and highlights evidence about the effectiveness of CMR in reducing PIPs.

Section 6.2 presents the overview of the modelling approach and the rationale for using a combination of two cohort models (decision tree model and Markov model). The structure of the decision tree model represents the immediate effect of CMR on prescribing and reduction of six PIPs. A six-state Markov transition model was chosen to link evidence about prescribing with the long-term effect on quality and length of life of patients.

Section 6.3 presents all the input parameters used in the model. The baseline mortality data for hospitalised patients with HF were extracted from the HES dataset as well as readmission rates for exacerbation of HF, falls and hyponatremia (HES, 2012). The model also incorporates data about potentially inappropriate prescribing and the effect on hospitalisation and mortality, based on the literature and evidence base of STOPP/START criteria (Gallagher *et al*., 2008; O'Mahony *et al*., 2010; O'Mahony *et al*., 2015). The cost of the medicines is taken from the British National Formulary (BNF, 2019) and the data from the ReMAC study described in chapter 3 (Szymanski *et al*., 2016; Ward *et al*., 2019). Finally, the model includes data on the impact of ADE on QALYs, by providing the utility values for hospitalisation from ADE and the cost of hospitalisation.

Section 6.4 showcases the results of the analysis. First, the results for base-case analysis are presented, followed by the results of a deterministic sensitivity analysis which entails best-worst case scenario analysis and analysis of the parameters with the greatest uncertainty (which were: effectiveness of CMR in reducing PIPs, type of PIPs used in the analysis, cost of substitute medicine prescribed instead of PIP and prevalence of PIPs). Finally, a probabilistic sensitivity analysis (PSA) was used to quantify the level of confidence in the output of the analysis. In the PSA, the parameters are represented by distributions and their value is drawn by random sampling from each distribution 10,000 times. The results are then plotted on a

cost-effectiveness acceptability curve and cost-effectiveness plane. The PSA was done for the base-case parameters, but also for parameters that were gathered from other sources. Finally, a subgroup analysis was conducted, and the results were presented for subpopulations based on age and severity of the disease.

Section 6.5 starts with a discussion of the results of the study in relation to the current literature. The discussion demonstrates how this study fills the gap in the literature and describes the generalisability of the results. The discussion emphasises the contribution of the study towards research on prescribing appropriateness, economic evaluation of interventions aimed at optimising healthcare and the health economics evaluation of complex intervention. The discussion suggests new priorities for further research in all these fields and ends by providing the strengths and limitations of the study.

Section 6.6 gives concluding remarks and provides the answer to the research question of the PhD.

6.1 Decision problem

6.1.1 Population

The population included in the model is all patients hospitalised with heart failure over the age of 70.

Heart failure is “a clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress” (European Society of Cardiology, 2016).

Heart failure (HF) was chosen as a target population in chapter 5 as described above and it meets the criteria set by NICE for a patient population that should receive CMR. HF is a common reason for admissions and readmissions to hospital including the emergency department and is one of the leading causes of in-hospital mortality. Patients with HF often have comorbidities (Bottle *et al*., 2014) and as such are often subject to polypharmacy to treat their multiple conditions. High cost of

treatment and high prevalence of PIPs were also considered when choosing the target population.

The age of patients entering the model in the base-case analysis was based on the current literature for heart failure. An analysis of four million data records from CPRD showed the average age of patient with HF in the UK was 77 years (Conrad *et al*., 2018). 70 years was chosen as the cut-off to capture the majority of HF patients in the UK. The prevalence of HF is around 1-2% of the population but it rises for patients 70 years or older, who have a prevalence of more than 10% (European Society of Cardiology, 2016). Data from the detailed UK annual heart failure audit (70,000 patient records each year) also confirm a steep rise in the prevalence of HF in patients over the age of 70 (NCAP, 2018). The study conducted in chapter 3 also includes patients aged 70 or more. The sensitivity analysis considered different age groups 60-64; 65-69; 70-74; 75-79; 80-84; ≥ 85-year olds. Subgroup analysis also considered how results change depending on the severity of HF, measured by the NYHA classification.

6.1.2 Intervention and comparators

The two interventions compared in the analysis were comprehensive medication review (CMR) and usual care. These are the same interventions described in chapter 4 for the short-term cost-effectiveness model. Chapter 4 provides details on the general characteristics of the two interventions.

The CMR aims to reduce potentially inappropriate prescribing (PIP) as a mechanism to improve health outcomes for the patient. The systematic literature review found that the two most commonly-used tools for conducting CMR were (1) Beers criteria and (2) Screening Tool of Older Person's Prescriptions/ Screening Tool to Alert doctors to Right Treatment, commonly known as STOPP/START criteria (Motter *et al*., 2018). Both were developed through a consensus of expert opinion, based on a Delphi process (as described in chapter 5, section 5.3.1.1 ‘potentially inappropriate prescribing’).

The CMR included in the analysis was a structured intervention using the STOPP/START criteria as a tool for determining the quality of prescribing. The choice of STOPP/START criteria as a structured approach to measuring PIPs in the

cost-utility model had several advantages. Firstly, the STOPP/START criteria were developed after Beers criteria to make more accurate assumptions about what PIPs are; for example, the STOPP/START criteria have significant association with ADE. Secondly, the STOPP/START criteria are appropriate for use in a hospital setting for older patients in acute care and can improve the appropriateness of medicines, with effects maintained up to six months after intervention. If the intervention is applied within 72 hours of admission, it reduces ADE by 9.3% and hospital length of stay by three days. Thirdly, the STOPP/START criteria look at both potential inappropriate medications (PIMs), hence the name 'STOPP' and potential prescribing omissions (PPOs), hence 'START'. Finally, the published evidence on the prevalence of PIP (measured by STOPP/START criteria) in the general population and patients with heart failure supported the rationale for the use of STOPP/START criteria (Gallagher *et al*., 2008; O'Mahony *et al*., 2010; O'Mahony *et al*., 2015; Ryan, 2011a).

The aim of STOPP/START criteria is to improve medication appropriateness, while preventing adverse drug events, and to reduce costs (Ryan, 2011a). The STOPP/START criteria were first developed in 2008 (Gallagher *et al*., 2008), with the aim to create a comprehensive list of potentially inappropriate prescriptions in older people for common health conditions. The list was based on the existing evidence and consensus of experts from geriatric and general medicine, clinical pharmacology, pharmacy and psychiatry. The tool was designed to be a practical asset for healthcare professional that could be easily used in daily practice. An updated version of STOPP/START was released in 2015 (O'Mahony et al., 2015). The update was necessary to ensure it reflected current evidence for existing medicines and included new medicines introduced into clinical practice in the intervening years. Version 2 includes a more comprehensive list of medicines, with additional and modified criteria added to the list. Version 2 was developed by a wider panel of experts from the UK and Ireland and from Europe.

6.1.3 Outcomes

The model was constructed in two parts which together form the long-term cost-utility model. The long-term cost-utility model is a combination of: (a) the decision tree model and (b) the Markov model. The decision tree model (a different model than the decision model from chapter 4) looked at an intermediate outcome, which was the

effectiveness of CMR in reducing PIPs. The Markov transition model looked at how the adverse drug events of these PIPs influenced the final patient outcome, so the quality and length of life of patients. The costs differed between the decision tree and Markov models to reflect costs at the different stages of patient care.

6.1.3.1 Intermediate outcome for clinical effectiveness in the decision tree model: Potentially inappropriate prescribing (PIPs)

Effectiveness of comprehensive medication review in reducing PIPs

The model will synthesise the evidence about the capacity of CMR to reduce PIPs (decision tree model) with the data about harmful effects of PIPs on quality and length of life (Markov model).

The most recent study on the effectiveness of CMR (using STOPP/START) to reduce PIPs is a systematic literature review with meta-analysis of randomised controlled trials (Hill-Taylor *et al*., 2016). Four RCTs were included in the meta-analysis (Dalleur *et al*., 2014; Frankenthal *et al*., 2014; Gallagher *et al*., 2011; García-Gollarte *et al*., 2014) that looked at improvement in potentially inappropriate medication rates. There were 1,935 patients included, all over 65 years of age, with one study including patients 75 years or older. The intervention included in the studies was a CMR applying STOPP/START criteria. All but one study (Dalleur *et al*., 2014) used the full list of 65 STOPP and 22 START criteria. Dalleur *et al*. excluded one STOPP and all the START criteria from the study. The comparator in all the studies was usual care.

The authors concluded that CMR done using the STOPP/START criteria may be effective in improving prescribing quality, humanistic clinical outcomes and economic outcomes (Hill-Taylor *et al*., 2016). The meta-analysis was conducted for rate of PIPs after the CMR or usual care was delivered. The odds ratio for the number of patients without PIPs was 2.98 (95%CI 1.30; 6.83) in favour of the CMR group.

Prevalence of PIPs in target population

The literature suggests that CMR reduces PIPs, but to conduct a cost-utility analysis it is important to establish the current prevalence of PIPs in the population of patients with HF.

There are many studies which report the prevalence of PIPs, however, there is large variation between the studies. The prevalence of PIPs will depend on a number of factors including the type of measurement used to estimate the prevalence (STOPP/START criteria, Beers criteria, etc.), the demographics and disease burden of the target population, the type of data used in analysis (routinely collected data or trial data) and the setting in which the study was conducted.

The prevalence of PIPs ranges from 21% to 79% of the general population of patients (Riordan *et al*., 2018). The literature review on the prevalence of PIPs in patients with HF, conducted in chapter 5, determined that the prevalence ranged from 15% to 58% of patients with HF.

Chapter 5 identified five studies that looked at prevalence of PIPs for patients with HF. The data for the model were taken from two key studies examining the prevalence of PIPs (measured using STOPP/START criteria):

1. (Bermingham *et al*., 2014)

   This study was selected as baseline data for modelling because it studied the prevalence of PIPs in hospitalised patients with HF measured by STOPP/START criteria and has the best estimates available in the literature for the correct target population; most other studies look at the general population of older patients or at specific populations other than heart failure.

   Other advantages of this study included: the size of the population, the fact that the population resembles the UK population, the hospital setting and, importantly, the fact that prevalence was measured using STOPP/START criteria.

   The study found that 57.7% of patients met at least one STOPP/START criterion during their stay at the hospital. Table 6.1 presents the six most common PIPs prescribed to patients with HF from this study. Each of the six PIPs represents at least 2% of all PIPs prescribed to patients with HF. The cost-utility model was constructed around these six criteria as a proxy of all the PIPs in patients with HF.

Table 6.1 Most common PIPs in patients with heart failure

STOPP criteria		Risk	Prevalence among all PIPs
1.	PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	Dose reduction or earlier discontinuation indicated	24%
2.	Benzodiazepines	Sedative, may cause reduced sensorium/impair balance	18.9%
3.	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	Optimisation of monotherapy within a single drug class should be observed prior to considering a new agent	4.9%
4.	Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatremia (i.e. serum Na+ < 130 mmol/l), hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	Hypokalaemia, hyponatremia, hypercalcaemia and gout can be precipitated by thiazide diuretic	2.9%
5.	NSAID with severe hypertension or severe heart failure	Risk of exacerbation of hypertension or heart failure	2.6%
6.	Neuroleptic drugs	May cause gait dyspraxia, Parkinsonism	2.6%

STOPP, Screening Tool of Older Person's Prescriptions; PIP, potentially inappropriate prescribing; NSAIDs, non-steroidal anti-inflammatory drugs; ACE inhibitors, angiotensin-converting-enzyme inhibitors; PPI, proton pump inhibitor; SSRIs, selective serotonin reuptake inhibitors Source: (Bermingham *et al*., 2014).

2. (Bradley *et al*., 2014)

The second study used for modelling measured the prevalence of PIPs in the general population. Bradley *et al*. looked at data from 1,019,491 people aged 70 years or older. The percentage of patients having at least one PIP (at least one of 52 STOPP criteria included in the analysis) was 29% (295,653 patients).

This study was used in the sensitivity analysis to understand the generalisability of the results to a broader population and to understand how that would affect the results. Although the study does not look only at patients with HF, it provides the best estimate of prevalence of PIPs in the UK general population. The study used CPRD data, a population health dataset which encompasses 35 million patients, with currently 11 million patients registered. CPRD data are primary care data that come from a network of GP practices from all over the UK. Among many health and demographic data collected in CPRD are data about prescriptions, information that is not found in the HES dataset.

6.1.3.2 Clinical effectiveness from the Markov model: hospitalisation, mortality and QALYs

The long-term clinical effectiveness outcome of the intervention was measured in quality-adjusted life years (QALYs). The main advantage of this approach is that QALYs measure both quality and length of life. This outcome measure is the preferred choice of NICE in the 'reference case' in the guide to the methods of technology appraisal (NICE, 2013b) because it combines data on mortality and morbidity into a single measure (Drummond *et al*., 2015). This allows for comparison between different health technologies as they have a common denominator. NICE uses a cost-effectiveness threshold of between £20,000 and £30,000 per one QALY gained, where health technologies that are within or below the threshold are usually approved. NICE recently introduced a fast track appraisal, where health technologies with a likely threshold below £10,000 per QALY would be deemed that they are offering exceptional value for money (McCabe *et al*., 2008; NICE, 2017; Timmins, 2017). Chapter 1 provides more information on what QALYs are, how they are calculated and how they are used.

In this study, QALYs were calculated based on utilities assigned to each Markov state. As the patients travel through the model, they collect utilities along the way. The utilities are collected for a period called a cycle, which in this model was one month. The utility weight was derived from the literature and presented in section 6.3.4 'Input parameter 4: Adverse events of potentially inappropriate prescribing' of this chapter. The utilities are based on EQ-5D questionnaires collected in different studies with similar populations and similar Markov health states. For the stable

heart failure state, the utilities were calculated by a study that used the time trade-off method (Matza *et al*., 2015).

6.1.3.3 Cost and resources

The cost of CMR intervention was assumed to be the same as in chapter 4. Cost was based on the average time needed for a pharmacist to complete a CMR and estimated at £25.20 per CMR. The other costs included in the model were the medicine costs for six groups of PIPs:

1. Proton pump inhibitors
2. Benzodiazepines
3. Any duplicate drug class prescription
4. Thiazide diuretic
5. NSAID
6. Neuroleptic drugs

The cost was estimated based on the British National Formulary (BNF) – the pharmaceutical reference book used in the UK NHS (see chapter 3). The BNF is widely used in cost-effectiveness analysis as the reference for all cost data related to prescribing. The costs used in the model are based on the drug tariff prices and include hospital prescribing (dispensed in the community and in hospital pharmacy departments) and primary care prescribing dispensed in the community. The costs are based on the net ingredient cost, which includes the basic price of a drug excluding VAT. The drug tariff price includes the amount paid to contractors for NHS Services for reimbursement (cost of medicines and appliances supplied against an NHS prescription form) and remuneration (professional fees and/or allowances paid as part of the NHS pharmacy contract) (PSNC, 2019).

The costs do not account for NHS negotiated discounts, which hospitals can often access. The costs also do not include patients' co-payments in the form of prescription charges (NHS Digital, 2018c).

The cost was calculated by using the following formula:

$$Monthly\ cost\ of\ medicine\ A = \left(\frac{Drug\ tariff\ price}{Number\ of\ units\ x\ \frac{Dose\ in\ 1\ unit}{SDD}} \right) x\ 30 \quad (6.1)$$

Units – tablets, capsules, ampoules etc; SDD – standard daily dose

The drug tariff prices included the average prices for oral capsules or tablets (if only other dosage forms were available, they were included in the analysis).

The costs of the appropriate alternative medicines prescribed instead of PIPs were based on data from ReMAC data that are presented in chapter 3. To calculate the costs of alternative medicines, I extracted ReMAC data for people with at least one of the six PIPs deprescribed and compared the cost of deprescribed medicines with the cost of started medicines. There were 83 patients who had at least one PIP deprescribed and had the full information on the cost of deprescribed and started medicines available. A dependent t-test was used to compare the mean cost between deprescribed and started medicines. The results of the test are presented in tables 6.2 and 6.3. On average, the cost of started medicines was greater ($\bar{x}$ = 16.43, SE = 1.76) than the cost of deprescribed medicines ($\bar{x}$ = 16.01, SE = 3.71). The difference £0.41 (95%CI; -5.85, 6.67) was not statistically significant, t(82) = 0.13, p = 0.90. The mean difference from the t-test was applied to the average cost of PIP to serve as the estimate of the cost of alternative medicines prescribed in place of PIP. The 95%CI was used in the probabilistic sensitivity analysis (PSA) to account for the uncertainty surrounding this value.

Table 6.2 Mean difference between STOPP and START medicines for patients with at least one PIP

	N	Mean	Standard deviation	Standard error mean
Cost STOPP	83	16.01	16.03	1.76
Cost START	83	16.43	33.78	3.71

Paired sample correlations correlation 0.53, $p \leq 0.000$

Table 6.3 Paired samples t-test comparing the cost of STOPP and START medicines for patients with at least one PIP

	Paired differences					t	df	p-value
	Mean	Standard deviation	Standard error mean	95%CI				
				Lower	Upper			
Cost START vs Cost STOPP	0.41	28.68	3.15	-5.85	6.67	0.13	82	0.90

CI, confidence Intervals; df, degrees of freedom; t, t-value; p-value, probability value

The costs in the decision tree model were limited to the cost of medicines and cost of delivering the CMR intervention that the patients were prescribed. In the long-term model the costs also included the cost of hospitalisation and long-term care for patients with HF. The model incorporates the cost of hospitalisation for three types of adverse drug events: exacerbation of HF, falls and hyponatremia estimated from the literature and routinely collected data of UK NHS reference costs. Unit costs were reported for a 2018 cost year and adjusted for inflation where necessary using the Bank of England inflation calculator. All other costs that could be related to treatment of the patients were assumed to be equal for both the CMR and usual care group and were not included in the analysis.

All the costs used in the model are presented in section 6.3 ‘Data sources’.

6.2 The cost-utility model

6.2.1 Model overview

The design of the study is a cost-utility analysis, where the measure of benefits is expressed in quality-adjusted life years (QALYs) and the costs are provided in pounds sterling. The perspective used in the model is the perspective of the payer, which is the UK NHS and PSS. Both benefits and costs are discounted at an equal rate of 3.5%, as per NICE 'reference case' (NICE, 2013b), which is the guideline of best practice for cost-effectiveness analysis in the NHS. In the sensitivity analysis the discount rate is changed to 1.5%, as per 'reference case'. The results are presented as the incremental cost-effectiveness ratio (ICER), which is calculated using formula 6.2.

$$ICER = \frac{\text{Cost of CMR} - \text{Cost of usual care (UC)}}{\text{QALY for CMR} - \text{QALY for UC}} \quad (6.2)$$

ICER – incremental cost-effectiveness ratio
CMR – comprehensive medication review
UC – usual care
QALY - quality-adjusted life year

6.2.2 Model structure

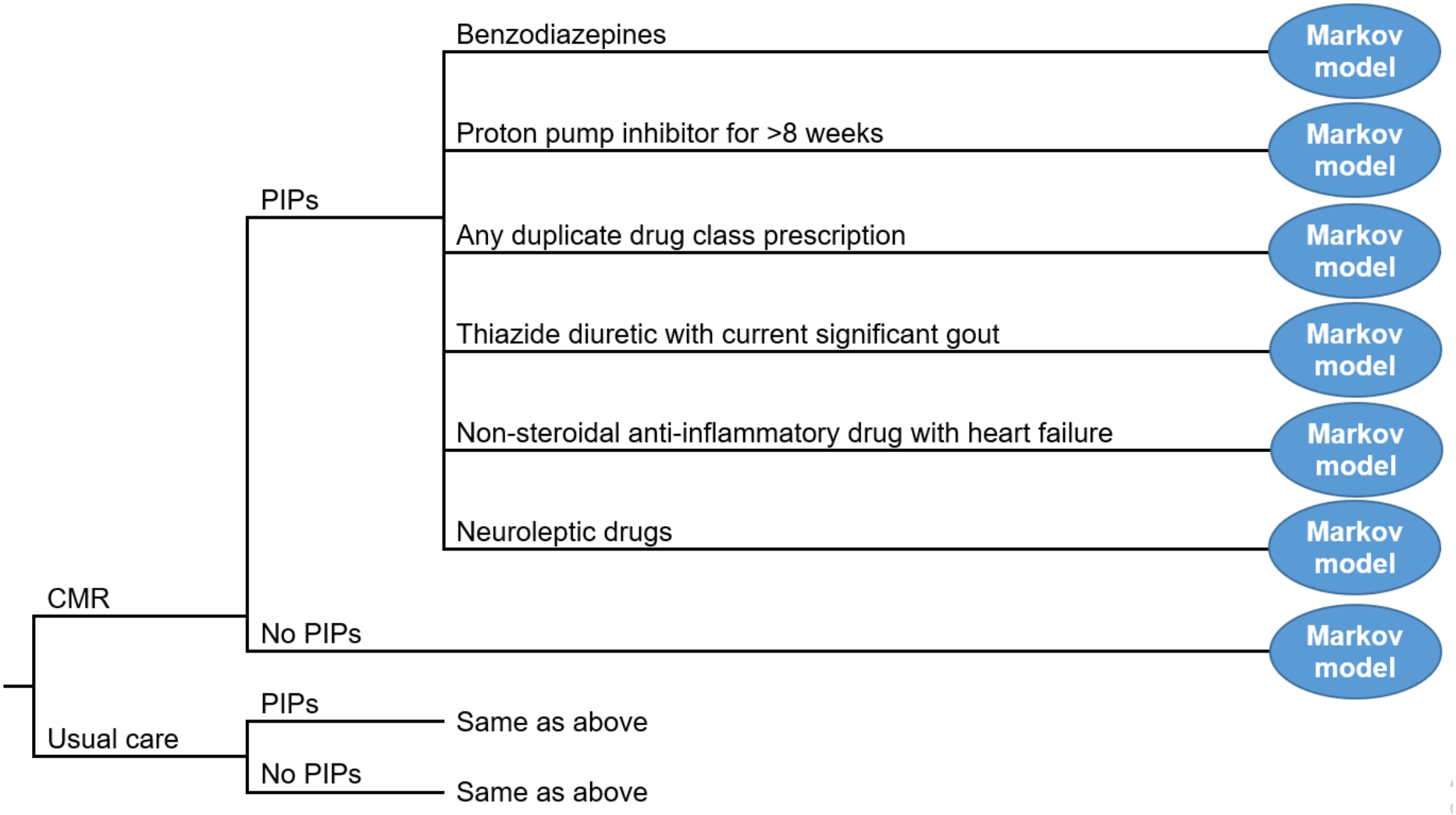
The cost-utility model is constructed in two complementary parts – a short-term decision tree model and a long-term Markov model. The model was constructed as two separate parts to combine two types of evidence. The models were developed using Microsoft Excel software.

Part 1 – the decision tree model (figure 6.1)

The decision tree model looks at the immediate effect of CMR on prescribing. The evidence that links CMR with reduction of PIPs is used in the decision tree model as in effect we know the chance that a patient will have a PIP and the type of PIP. Decision tree models are usually used when the timeframe is short, the process is not complicated, the recurrence of events does not matter and there is no interaction between patients (example of interaction can be infection from communicable disease) (Hoang *et al*., 2016). In this chapter, the decision tree model is used to look

at the effect of CMR on prescribing within a short period of time from when a patient makes an initial hospital visit and enters the model, which makes the decision tree model the most appropriate in this situation. The decision tree model looks at the cost and effects over a one-month time horizon, during which time the patient has the initial hospitalisation and can either receive usual care or CMR. Each of the branches (CMR and usual care) leads to a chance node. Chance will determine whether a patient (1) will avoid a potentially inappropriate prescription (no PIP) or (2) will receive a PIP. The branch will then lead to a specific PIP. The literature provides the most common PIPs in patients with HF (table 6.1) and their prevalence (Bermingham *et al*., 2014; Bradley *et al*., 2014). Systematic literature review with meta-analysis showed that CMR may reduce the number of patients with PIP (measured by STOPP/START criteria) with odds ratio of 2.98 (95%CI 1.30; 6.83) in favour of the CMR group.

Figure 6.1 Short-term decision tree model structure



Part 2 – the Markov model (figure 6.2)

The second part of the model is the Markov model. The Markov model answers the question of what happens to the patients after they receive PIP. In health economics, Markov models are used when the events can repeat, the order of these events is important, and the timeframe is longer (Drummond *et al*., 2015).

In this decision problem the events can repeat, as hospitalised patients with heart failure can have multiple readmissions. Therefore, the ability of the Markov model to repeat the events is important. The patient can also experience adverse effects of the medicines not just once, but multiple times throughout their life.

The order of the events is also important, as the patient's readmission needs to follow the patient's initial hospitalisation and subsequent discharge; only then can readmission occur.

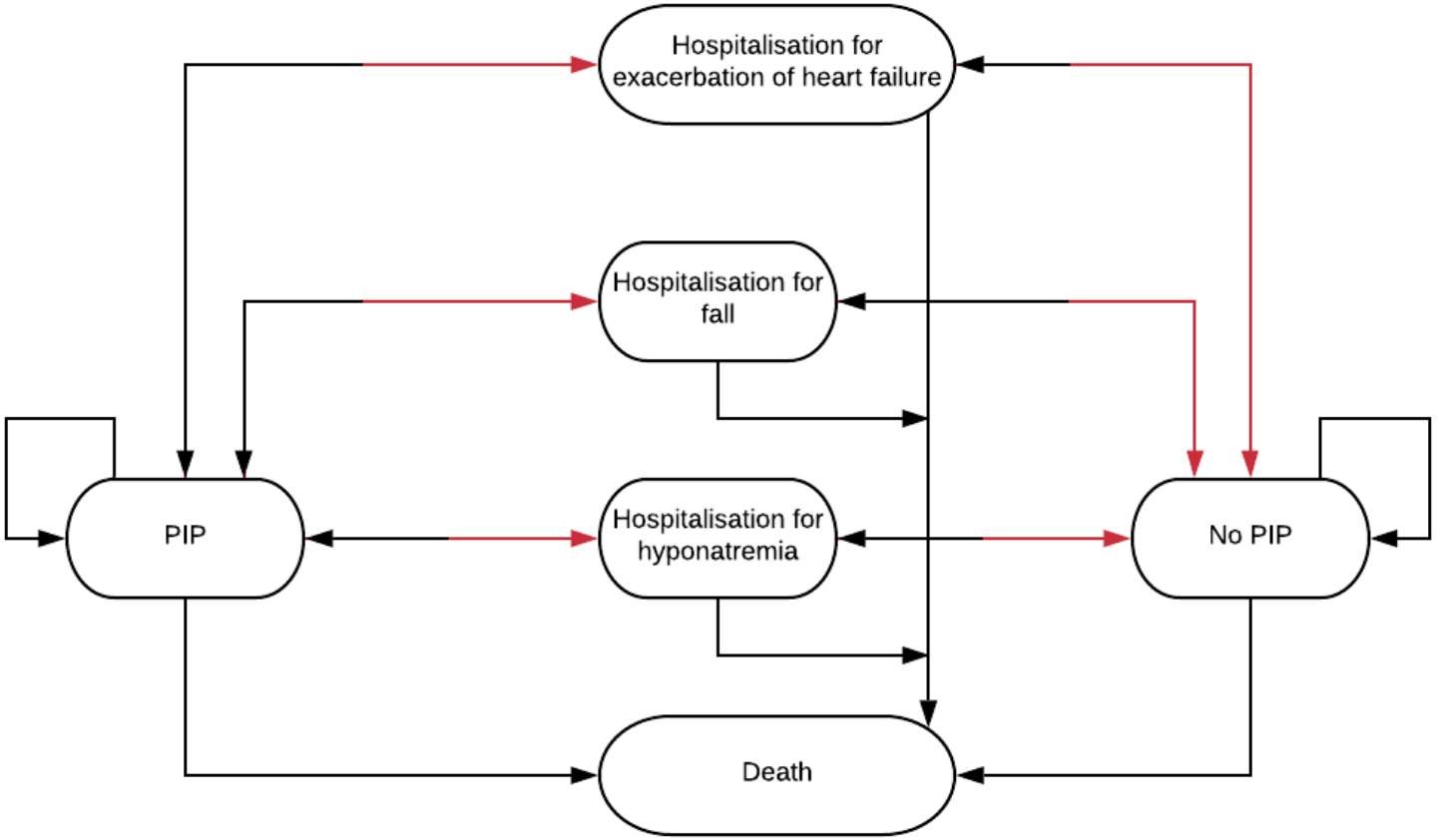
The Markov model was also used because patients on PIP can use health service resources for treatment of negative effects of PIP for the remainder of their lives. The effectiveness of CMR in reducing PIPs can also impact on the cost that the patient generates throughout his life. To compare the cost-utility of CMR vs usual care it is also necessary to present the benefits in terms of a patient health outcome, in this case QALY. Calculating QALYs requires estimating the survival duration of the patients and therefore a long-term model is needed. Because the Markov model used in this chapter looks at the long-term effects of having or not having a PIP on a patient's health and at what cost, it was appropriate to use this type of model.

The model takes the form of a four-state Markov process, with a cycle length of one month. The model uses a lifetime horizon and it was run for 300 cycles, equivalent to 25 years, by which time the survival for patients was approximating 0. The decision tree model determines where the patients enter the Markov model. Depending on the progress in the decision tree model, patients enter the model in a 'stable HF on PIP' state or 'stable HF not on PIP' state. Patients in both states will have a probability of moving from stable HF to dead state or having one of three possible adverse drug events which result in a hospitalisation event. The three ADEs as described before are:

a) exacerbation of heart failure;
b) fall;
c) hyponatremia.

From each of the hospitalisation events patients are assumed to revert to ‘stable HF on PIP’ or ‘stable HF not on PIP’. The baseline probability of death and hospitalisation for HF patients comes from HES data. For each of the six PIPs, the increased risk of mortality or hospitalisation for the three adverse drug events is applied to the baseline probability. Each Markov state has a cost value and utility value attached to that state.

Figure 6.2 Markov model structure



6.3 Data sources

6.3.1 Input parameter 1: Mortality data

The cost-utility model incorporates monthly mortality risk for patients with HF based on Hospital Episode Statistics, which is a data warehouse containing data about admissions to NHS hospitals in England. HES data contain more than 200 million records, with each record containing a substantial amount of information about individual patients including demographic data, clinical information about the admission and procedures carried out during the admission (HERC Oxford University, 2019a).

A subset of HES data was used for a study conducted at the Primary Care and Public Health (PCPH) Department of Imperial College London. The study looked at factors associated with hospital emergency readmission and mortality rates in patients with heart failure or chronic obstructive pulmonary disease (Bottle, Honeyford, *et al*., 2018). The PCPH Department provided me with an extract from the dataset including mortality and hospital readmission data for patients with heart failure based on 3,440,941 admissions to NHS hospitals from April 2013 to March 2015 (table 6.4).

Table 6.4 Mortality of hospitalised patients with heart failure

Age band	Number of patients	Number of deaths
0-4	1,306	21
5-9	672	16
10-14	674	13
15-19	1,991	45
20-24	4,044	76
25-29	5,467	68
30-34	8,887	120
35-39	13,573	209

40-44	26,494	333
45-49	49,777	679
50-54	81,042	1,283
55-59	115,714	2,081
60-64	176,297	3,874
65-69	276,907	7,301
70-74	370,044	1,568
75-79	536,994	19,741
80-84	666,767	30,896
85-89	629,333	36,763
≥ 90	474,958	37,525

6.3.2 Input parameter 2: Hospitalisation

The second parameter was the monthly risk of hospitalisation for patients with heart failure discharged from their initial index hospital visit. The baseline risk of hospitalisation was derived from the same subset of HES data as the mortality risk. The hospitalisation risk was based on one-year readmission rates following the patient's index admission for HF. The index admission was defined as any admission with a primary diagnosis ICD-10 code of I50. The subsequent readmission was defined as first readmission of patient to hospital, within one year of the index admission, with a diagnosis of:

- Exacerbation of HF – (ICD-10 code: I50);
- Falls – (ICD-10 codes: W00-W19);
- Hyponatremia – (ICD-10 code: E87.1).

The rates of one-year readmissions were converted to monthly probabilities of patients being readmitted. Table 6.5 presents data included in the model and the probabilities of all-cause readmissions and all-cause emergency readmissions.

Table 6.5 Hospitalisation for patients with heart failure

Age band	Number of patients	All-cause readmissions	All-cause emergency readmissions	Readmissions for HF	Readmissions for falls	Readmissions for hyponatremia
0-4	1,306	582	272	16	1	5
5-9	672	199	90	2	1	1
10-14	674	284	113	4	0	10
15-19	1,991	782	201	12	1	3
20-24	4,044	848	429	26	5	5
25-29	5,467	1,206	632	44	5	8
30-34	8,887	1,606	814	61	5	9
35-39	13,573	2,820	1,667	119	21	14
40-44	26,494	5,248	3,251	245	36	62
45-49	49,777	9,506	5,769	481	61	108
50-54	81,042	15,895	9,525	919	154	219
55-59	115,714	22,135	13,069	1,312	234	343
60-64	176,297	34,865	20,764	2,076	437	569
65-69	276,907	54,964	33,399	3,476	923	883

Age band	Number of patients	All-cause readmissions	All-cause emergency readmissions	Readmissions for HF	Readmissions for falls	Readmissions for hyponatremia
70-74	370,044	74,216	46,273	5,050	1,560	1,245
75-79	536,994	102,508	67,638	7,532	3,087	1,929
80-84	666,767	119,532	86,357	9,679	5,580	2,661
85-89	629,333	104,673	83,351	9,020	7,152	2,861
≥ 90	474,958	71,200	61,934	6,480	6,589	2,172

6.3.3 Input parameter 3: Potentially inappropriate prescribing

The third set of parameters included in the model related to the data about six potentially inappropriate prescriptions (PIPs). The parameters included the cost of the PIPs and their adverse drug events including increasing mortality and hospitalisation.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are used with an indication of relieving pain and reducing inflammation and high temperature. NSAIDs work by inhibiting the cyclo-oxygenase-1 (COX-1) and COX-2 enzymes. These enzymes are involved in synthesis of prostaglandins, which are mediators of pain and inflammation. This gives the NSAID anti-inflammatory, antipyretic and analgesic effects. The synthesis of prostaglandins occurs in the blood vessel wall and increases blood flow by relaxing the blood vessels. Most NSAIDs are sold as over-the-counter medicines (BNF, 2019; Encyclopaedia Britannica, 2018).

NSAIDs can be divided into two groups:

1. Non-selective NSAIDs – older generation of medicines that inhibit COX-1 and COX-2
2. Selective NSAIDs – newer generation that influence only COX-2.

(BNF, 2019; Encyclopaedia Britannica, 2018)

<u>STOPP/START criteria</u>

H2. NSAID with established hypertension (risk of exacerbation of hypertension) or heart failure (risk of exacerbation of heart failure) (O'Mahony *et al*., 2015).

<u>NSAID used in the analysis:</u>

- Celecoxib;
- Ibuprofen;
- Diclofenac;
- Naproxen.

Increased mortality and hospitalisation

NSAIDs are associated with increased mortality and morbidity for patients with heart failure. They are still commonly prescribed for people with heart failure, but this should only happen if the benefit of the medicine outweighs the risk. Table 6.6 presents the increased risk of all-cause mortality and hospitalisation due to exacerbation of heart failure for patients with HF on NSAIDs. The risk is presented as a hazard ratio (HR), which is the ratio of the chances of a certain event occurring (in this case death or hospitalisation) in two groups (in this case patients on NSAID and patients not on NSAID) at a given interval of time. HR that equals 1 means there is no association; HR > 1 means the risk is increased; HR < 1 means the risk is smaller.

Table 6.6 Hazard ratios for increased risk of death and hospitalisation for HF among NSAID users

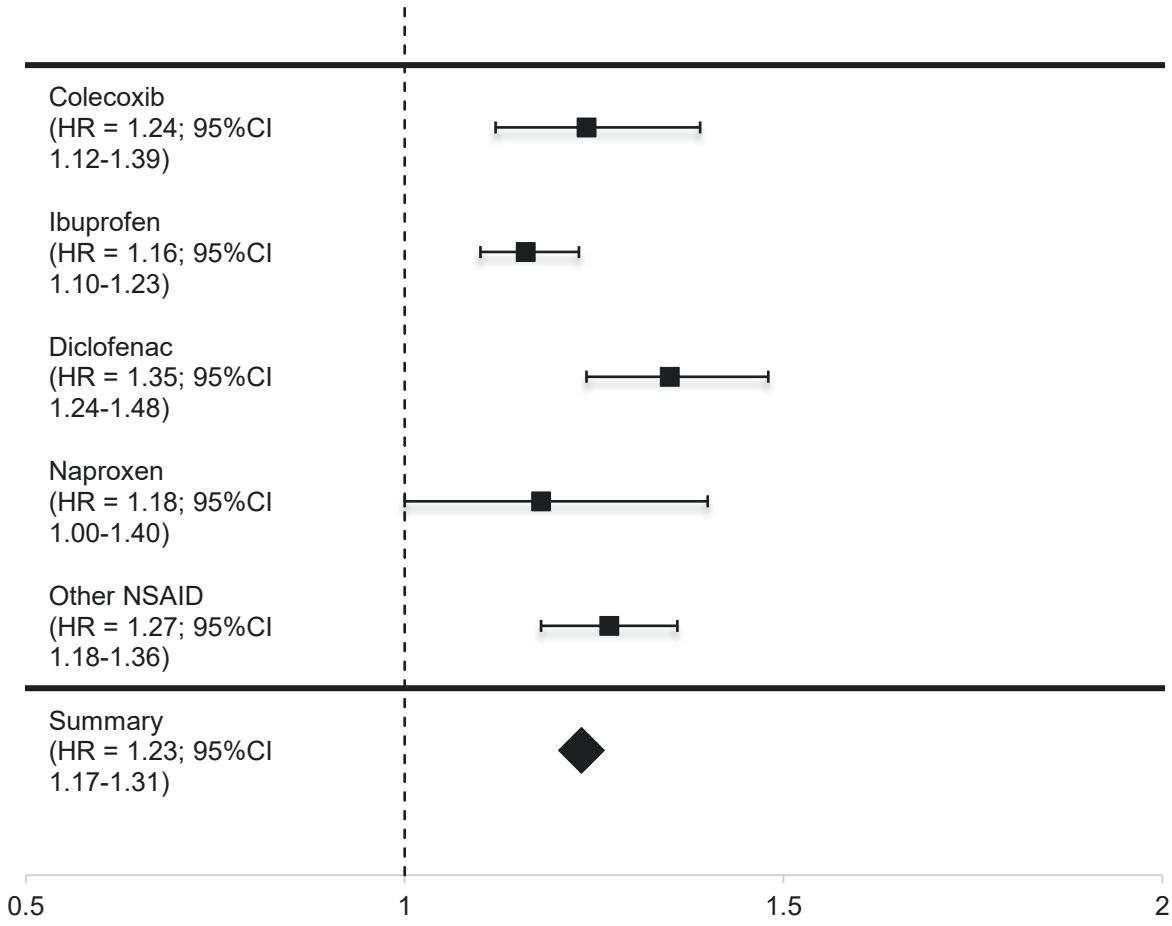
Medicine	All-cause mortality		Hospitalisation due to exacerbation of heart failure	
	Hazard ratio (95%CI)	P value[1]	Hazard ratio (95%CI)	P value[1]
Celecoxib	1.75 (1.63; 1.88)	< 0.001	1.24 (1.12; 1.39)	< 0.001
Ibuprofen	1.31 (1.25; 1.37)	< 0.001	1.16 (1.10; 1.23)	< 0.001
Diclofenac	2.08 (1.95; 2.21)	< 0.001	1.35 (1.24; 1.48)	< 0.001
Naproxen	1.22 (1.07; 1.39)	0.004	1.18 (1.00; 1.40)	0.05
Other NSAIDs	1.28 (1.21; 1.35)	< 0.001	1.27 (1.18; 1.36)	< 0.001

CI, confidence Interval; NSAIDs, non-steroidal anti-inflammatory drugs
[1] - Cox proportional-hazard adjusted for gender, age, comorbidity, first hospitalisation for heart failure, loop diuretic dose, other medical treatment
Source: (Gislason *et al*., 2009)

To determine the hazard ratio for the NSAID drugs combined, I conducted a meta-analysis of the data from table 6.6 published by (Gislason *et al*., 2009).

The results from the meta-analysis (figure 6.3) for increased hospitalisation for exacerbation of HF for NSAID users was HR = 1.23 (95%CI, 1.17-1.31). The results were statistically significant, with moderate heterogeneity between the HR for different NSAIDs included in the meta-analysis.

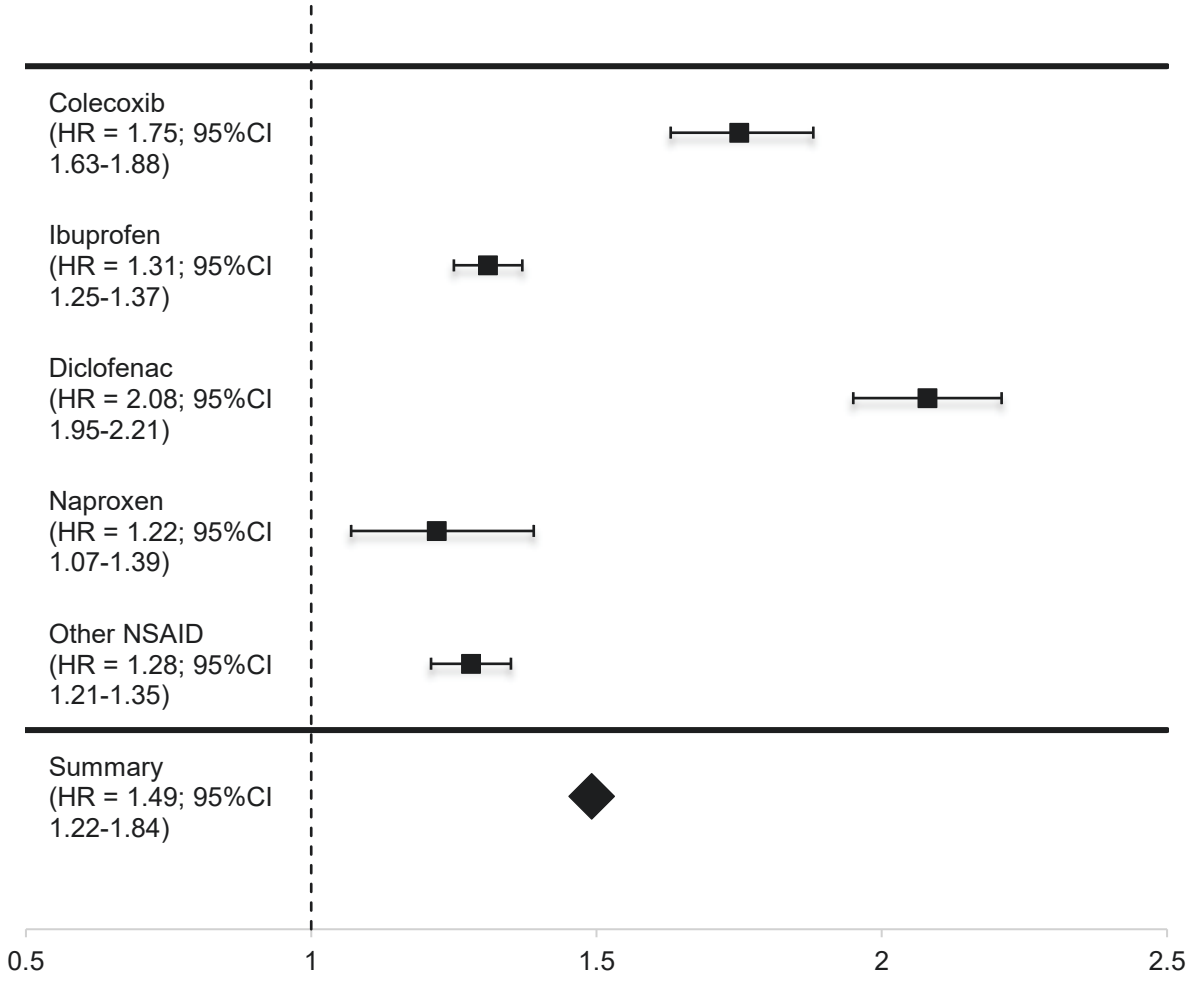
Figure 6.3 Results of meta-analysis of HR for increased hospitalisation for exacerbation of HF associated with NSAID use



Heterogeneity: I-squared = 56.49%, tau-squared = 0.0496, p = 0.0496
Source: Based on data from (Gislason *et al.*, 2009)

The results of the meta-analysis (figure 6.4) for increased risk of mortality for NSAID users was HR = 1.49 (95%CI, 1.22-1.84). The results were statistically significant, however there was marked heterogeneity between the HR for different NSAIDs included in the meta-analysis. This means that different NSAIDs increase the risk of death at different rates, with naproxen having the lowest HR at 1.22 (95%CI; 1.07-1.39) and diclofenac the highest HR at 2.08 (95%CI; 1.95-2.21). The results suggest that there is an increased risk of mortality for patients with HF using NSAIDs, however the magnitude of the effect depends on the type of medicine. To account for that uncertainty, the results were tested in sensitivity analysis where the extreme values were tested for the highest and lowest risk of death.

Figure 6.4 Results of meta-analysis of HR for increased mortality associated with NSAID use



Heterogeneity: I-squared = 98.02%, tau-squared = 0.2293, p < 0.0001
Source: Based on data from (Gislason *et al.*, 2009)

Cost of NSAIDs in the UK NHS

The cost of NSAIDs was derived from the BNF and costs were calculated based on formula 6.1. Please refer to section 6.1.3.3 of this chapter for more information. The cost of NSAIDs used in the model was the average of medicines presented in table 6.7 ($\bar{x}$ = £19.10, SE = 4.54).

Table 6.7 The costs of different NSAID medicines available in the UK NHS

Dosage forms	Medicine concentration per unit	Standard daily dose	Drug tariff	Number of units	Monthly cost
Celecoxib					
Capsule	100 mg	200 mg	£2.72	60 capsules	£2.72
	200 mg	200 mg	£1.01	30 capsules	£1.01
Ibuprofen					
Tablet	200 mg	900 mg	£2.77	84 tablets	£4.45
	200 mg	1,600 mg	£2.77	84 tablets	£7.91
	600 mg	900 mg	£4.03	84 tablets	£2.16
	600 mg	1,600 mg	£4.03	84 tablets	£3.84
Orodispersible tablet*	200 mg	900 mg	£2.58	12 tablets	£29.03
	200 mg	1,600 mg	£2.58	12 tablets	£51.60
Modified-release tablet*	800mg	1,600 mg	£7.74	56 tablets	£8.29
Capsule	200 mg	900 mg	£4.53	30 capsules	£20.39
	200 mg	1,600 mg	£4.53	30 capsules	£36.24
	400 mg	900 mg	£6.14	20 capsules	£20.72
	400 mg	1,600 mg	£6.14	20 capsules	£36.84
Modified-release capsule*	300 mg	1,600 mg	£4.52	24 capsules	£30.13
Effervescent granules*	600 mg	900 mg	£6.80	20 sachets	£15.30
	600 mg	1,600 mg	£6.80	20 sachets	£27.20
Oral suspension syrup*	100mg/5ml	900 mg	£8.88	500 ml	£23.98
	100mg/5ml	1,600 mg	£8.88	500 ml	£42.62
Oral suspension sachets*	100mg/5ml	900 mg	£2.42	12 sachets	£54.45
	100mg/5ml	1,600 mg	£2.42	12 sachets	£96.80
Gel*	5% gel	900 mg	£2.26	100 g	£12.20

	5% gel	1,600 mg	£2.26	100 g	£21.70
	5% gel	900 mg	£1.13	50 g	£12.20
	5% gel	1,600 mg	£1.13	50 g	£21.70
	10% gel	900 mg	£5.79	100 g	£15.63
	10% gel	1,600 mg	£5.79	100 g	£27.79
Diclofenac					
Mouthwash	0.74 mg/ml	30 ml	£12.95	200 ml	£58.28
	0.74 mg/ml	45 ml	£12.95	200 ml	£87.41
Naproxen					
Tablet	250 mg	500 mg	£1.51	28 tablets	£3.24
	250 mg	1,000 mg	£1.51	28 tablets	£6.47
	500 mg	500 mg	£7.27	28 tablets	£7.79
	500 mg	1,000 mg	£7.27	28 tablets	£15.58
Effervescent tablet*	250 mg	500 mg	£52.72	20 tablets	£158.16
	250 mg	1,000 mg	£52.72	20 tablets	£316.32
Gastro-resistant tablet	250 mg	500 mg	£7.23	56 tablets	£7.75
	250 mg	1,000 mg	£7.23	56 tablets	£15.49
	375 mg	500 mg	£27.62	56 tablets	£19.73
	375 mg	1,000 mg	£27.62	56 tablets	£39.46
	500 mg	500 mg	£14.10	56 tablets	£7.55
	500 mg	1,000 mg	£14.10	56 tablets	£15.11
Oral suspension*	125mg/5ml	500 mg	£119.00	100 ml	£714.00
	125mg/5ml	1,000 mg	£119.00	100 ml	£1,428.00
	50 mg/ml	500 mg	£45.03	100 ml	£135.09
	50 mg/ml	1,000 mg	£45.03	100 ml	£270.18

* Costs used in the sensitivity analysis.
mg – milligram; ml – millilitre.
The costs calculated based on (BNF, 2019).

Neuroleptic drugs

Neuroleptics are antipsychotic medications used in psychiatric disorders. They are used to treat and manage symptoms of psychosis, acute mania, bipolar disorder, hyperactivity, acute mania, Tourette syndrome, agitation, attention-deficit hyperactivity disorder (ADHD), depression, eating disorders, insomnia, obsessive-compulsive disorder, anxiety, behavioural disturbances in dementia, substance use, dependence disorders, post-traumatic stress disorder (PTSD) and personality disorders (Sangani & Saadabadi, 2019).

There are two classes of neuroleptic drugs:

1. First-generation – 'typical'
   The first-generation neuroleptics work by postsynaptic blockade of dopamine D2 receptors in the central nervous system.
2. Second-generation – 'atypical'
   The second-generation neuroleptics have a different mechanism of action, in which they transiently occupy the D2 receptors and then quickly dissociate to allow a normal dopamine neurotransmission.

(Sangani & Saadabadi, 2019).

<u>STOPP/START criteria</u>

K2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).

(O'Mahony *et al*., 2015)

<u>Increased hospitalisation</u>

The association between neuroleptics and falls has been studied through a meta-analysis of four studies with 13,140 participants. The increased risk of falling among the elderly was presented as a Bayesian adjusted odds ratio of 1.39 (95%CI 0.94; 2.00).

(Hill & Wee, 2012; Woolcott *et al*., 2009)

Increased mortality

For increased risk of mortality following a major fall, see 'Falls' section in section 6.3.4 'Input parameter 4: Adverse events of potentially inappropriate prescribing'

Cost of neuroleptics in the UK NHS

Table 6.8 presents the different types and forms of neuroleptic drugs available in the UK NHS. For the model the average cost of these medicines was included ($\bar{x}$ = £26.09; SE = 0.65).

Table 6.8 The costs of different neuroleptic drugs available in the UK NHS

Dosage forms	Medicine concentration per unit	Standard daily dose	Drug tariff	Number of units	Monthly cost
Chlorpromazine hydrochloride					
Tablet	25 mg	25 mg	£41.72	28 tablets	£44.70
	25 mg	100 mg	£41.72	28 tablets	£178.80
	50 mg	25 mg	£41.81	28 tablets	£22.40
	50 mg	100 mg	£41.81	28 tablets	£89.59
	100 mg	25 mg	£41.56	28 tablets	£11.13
	100 mg	100 mg	£41.56	28 tablets	£44.53
Oral solution*	25 mg/5 ml	25 mg	£2.35	150 ml	£2.35
	25 mg/5 ml	100 mg	£2.35	150 ml	£9.40
	100 mg/5 ml	25 mg	£5.50	150 ml	£1.38
	100 mg/5 ml	100 mg	£5.50	150 ml	£5.50
Levomepromazine					
Tablet	100 mg	6 mg	£20.26	84 tablets	£0.43
	100 mg	200 mg	£20.26	84 tablets	£14.47
Solution for injection*	25 mg/1 ml	6.25 mg	£20.13	10 ampoules	£15.10
	25 mg/1 ml	50 mg	£20.13	10 ampoules	£120.78

Promazine hydrochloride					
Tablet	25 mg	100 mg	£45.34	100 tablets	£54.41
	25 mg	200 mg	£45.34	100 tablets	£108.82
	50 mg	100 mg	£76.18	100 tablets	£45.71
	50 mg	200 mg	£76.18	100 tablets	£91.42
Oral solution*	25 mg/5 ml	100 mg	£15.00	150 ml	£60.00
	25 mg/5 ml	200 mg	£15.00	150 ml	£120.00
	50 mg/5 ml	100 mg	£17.00	150 ml	£34.00
	50 mg/5 ml	200 mg	£17.00	150 ml	£68.00
Pericyazine					
Tablet	2.5 mg	15 mg	£27.90	84 tablets	£59.79
	2.5 mg	70 mg	£27.90	84 tablets	£279.00
	10 mg	15 mg	£72.00	84 tablets	£38.57
	10 mg	70 mg	£72.00	84 tablets	£180.00
Oral solution*	10 mg/5 ml	15 mg	£82.80	100 ml	£186.30
	10 mg/5 ml	70 mg	£82.80	100 ml	£869.40
Fluphenazine decanoate					
Solution for injection	25 mg/1 ml	0.4 mg	£22.55	10 ampoules	£1.08
	25 mg/1 ml	7.1 mg	£22.55	10 ampoules	£19.21
	100 mg/1 ml	0.4 mg	£43.73	5 ampoules	£1.05
	100 mg/1 ml	7.1 mg	£43.73	5 ampoules	£18.63
Prochlorperazine					
Tablet	5 mg	10 mg	£0.73	28 tablets	£1.56
	5 mg	100 mg	£0.73	28 tablets	£15.64
Buccal tablet*	3 mg	6 mg	£37.23	50 tablets	£44.68
	3 mg	12 mg	£37.23	50 tablets	£89.35

Oral solution*	5 mg/5 ml	10 mg	£3.34	100 ml	£10.02
	5 mg/5 ml	100 mg	£3.34	100 ml	£100.20
Solution for injection*	12.5 mg/1 ml	12.5 mg	£5.23	10 ampoules	£15.69
	12.5 mg/1 ml	75 mg	£5.23	10 ampoules	£94.14
Trifluoperazine					
Tablet	1 mg	2 mg	£59.12	112 tablets	£31.67
	1 mg	10 mg	£59.12	112 tablets	£158.36
	5 mg	2 mg	£134.89	112 tablets	£14.45
	5 mg	10 mg	£134.89	112 tablets	£72.26
Oral solution*	1 mg/5 ml	2 mg	£112.25	200 ml	£168.38
	1 mg/5 ml	10 mg	£112.25	200 ml	£841.88
	5 mg/5 ml	2 mg	£27.00	150 ml	£10.80
	5 mg/5 ml	10 mg	£27.00	150 ml	£54.00
Benperidol					
Tablet	250 µg	0.125 mg	£117.31	112 tablets	£15.71
	250 µg	0.75 mg	£117.31	112 tablets	£94.27
Flupentixol					
Tablet	500 µg	0.5 mg	£2.88	60 tablets	£1.44
	500 µg	9 mg	£2.88	60 tablets	£25.92
	1 mg	0.5 mg	£4.86	60 tablets	£1.22
	1 mg	9 mg	£4.86	60 tablets	£21.87
	3 mg	0.5 mg	£13.92	100 tablets	£0.70
	3 mg	9 mg	£13.92	100 tablets	£12.53
Haloperidol					
Tablet	500 µg	0.25 mg	£29.59	28 tablets	£15.85
	500 µg	2.5 mg	£29.59	28 tablets	£158.52

	1.5 mg	0.25 mg	£15.10	28 tablets	£2.70
	1.5 mg	2.5 mg	£15.10	28 tablets	£26.96
	5 mg	0.25 mg	£16.50	28 tablets	£0.88
	5 mg	2.5 mg	£16.50	28 tablets	£8.84
	10 mg	0.25 mg	£19.36	28 tablets	£0.52
	10 mg	2.5 mg	£19.36	28 tablets	£5.19
Capsule	500 µg	0.25 mg	£1.18	30 capsules	£0.59
	500 µg	2.5 mg	£1.18	30 capsules	£5.90
Oral solution*	5 mg/5 ml	0.25 mg	£6.47	100 ml	£0.49
	5 mg/5 ml	2.5 mg	£6.47	100 ml	£4.85
	2 mg/ml	0.25 mg	£7.10	100 ml	£0.27
	2 mg/ml	2.5 mg	£7.10	100 ml	£2.66
Solution for injection*	5 mg/ml	0.5 mg	£35.00	10 ampoules	£10.50
Pimozide					
Tablet	4 mg	2 mg	£40.31	100 tablets	£6.05
	4 mg	20 mg	£40.31	100 tablets	£60.47
Sulpiride					
Tablet	200 mg	400 mg	£4.40	30 tablets	£8.80
	400 mg	400 mg	£18.80	30 tablets	£18.80
Oral solution*	200 mg/5 ml	400 mg	£31.00	150 ml	£62.00
Zuclopenthixol					
Tablet	2 mg	20 mg	£3.14	100 tablets	£9.42
	2 mg	50 mg	£3.14	100 tablets	£23.55
	10 mg	20 mg	£8.06	100 tablets	£4.84
	10 mg	50 mg	£8.06	100 tablets	£12.09
	25 mg	20 mg	£16.13	100 tablets	£3.87

	25 mg	50 mg	£16.13	100 tablets	£9.68
Amisulpride					
Tablet	50 mg	50 mg	£6.02	60 tablets	£3.01
	50 mg	800 mg	£6.02	60 tablets	£48.16
	100 mg	50 mg	£8.73	60 tablets	£2.18
	100 mg	800 mg	£8.73	60 tablets	£34.92
	200 mg	50 mg	£13.71	60 tablets	£1.71
	200 mg	800 mg	£13.71	60 tablets	£27.42
	400 mg	50 mg	£42.05	60 tablets	£2.63
	400 mg	800 mg	£42.05	60 tablets	£42.05
Oral solution*	100 mg/ml	50 mg	£49.44	60 ml	£12.36
	100 mg/ml	800 mg	£49.44	60 ml	£197.76
Aripiprazole					
Tablet	5 mg	10 mg	£1.71	28 tablets	£3.66
	5 mg	15 mg	£1.71	28 tablets	£5.50
	10 mg	10 mg	£1.51	28 tablets	£1.62
	10 mg	15 mg	£1.51	28 tablets	£2.43
	15 mg	10 mg	£1.63	28 tablets	£1.16
	15 mg	15 mg	£1.63	28 tablets	£1.75
	30 mg	10 mg	£12.25	28 tablets	£4.38
	30 mg	15 mg	£12.25	28 tablets	£6.56
Orodispersible tablet*	10 mg	10 mg	£79.22	28 tablets	£84.88
	10 mg	15 mg	£79.22	28 tablets	£127.32
Oral solution*	1 mg/ml	10 mg	£101.05	150 ml	£202.10
	1 mg/ml	15 mg	£101.05	150 ml	£303.15

Clozapine					
Tablet	25 mg	50 mg	£3.02	28 tablets	£6.47
	25 mg	450 mg	£3.02	28 tablets	£58.24
	25 mg	50 mg	£8.40	84 tablets	£6.00
	25 mg	450 mg	£8.40	84 tablets	£54.00
	25 mg	50 mg	£10.00	100 tablets	£6.00
	25 mg	450 mg	£10.00	100 tablets	£54.00
	100 mg	50 mg	£12.07	28 tablets	£6.47
	100 mg	450 mg	£12.07	28 tablets	£58.19
	100 mg	50 mg	£33.60	84 tablets	£6.00
	100 mg	450 mg	£33.60	84 tablets	£54.00
	100 mg	50 mg	£39.00	100 tablets	£5.85
	100 mg	450 mg	£39.00	100 tablets	£52.65
Olanzapine					
Tablet	2.5 mg	5 mg	£1.09	28 tablets	£2.34
	2.5 mg	20 mg	£1.09	28 tablets	£9.34
	5 mg	5 mg	£1.27	28 tablets	£1.36
	5 mg	20 mg	£1.27	28 tablets	£5.44
	7.5 mg	5 mg	£1.65	28 tablets	£1.18
	7.5 mg	20 mg	£1.65	28 tablets	£4.71
	10 mg	5 mg	£1.28	28 tablets	£0.69
	10 mg	20 mg	£1.28	28 tablets	£2.74
	15 mg	5 mg	£1.69	28 tablets	£0.60
	15 mg	20 mg	£1.69	28 tablets	£2.41
	20 mg	5 mg	£2.11	28 tablets	£0.57
	20 mg	20 mg	£2.11	28 tablets	£2.26

Orodispersible tablet*	5 mg	5 mg	£26.52	28 tablets	£28.41
	5 mg	20 mg	£26.52	28 tablets	£113.66
	5 mg	5 mg	£4.71	28 tablets	£5.05
	5 mg	20 mg	£4.71	28 tablets	£20.19
	10 mg	5 mg	£44.62	28 tablets	£23.90
	10 mg	20 mg	£44.62	28 tablets	£95.61
	10 mg	5 mg	£6.46	28 tablets	£3.46
	10 mg	20 mg	£6.46	28 tablets	£13.84
	15 mg	5 mg	£45.43	28 tablets	£16.23
	15 mg	20 mg	£45.43	28 tablets	£64.90
	15 mg	5 mg	£6.97	28 tablets	£2.49
	15 mg	20 mg	£6.97	28 tablets	£9.96
	20 mg	5 mg	£74.24	28 tablets	£19.89
	20 mg	20 mg	£74.24	28 tablets	£79.54
	20 mg	5 mg	£8.84	28 tablets	£2.37
	20 mg	20 mg	£8.84	28 tablets	£9.47
Oral lyophilizate*	5 mg	5 mg	£48.07	28 tablets	£51.50
	5 mg	20 mg	£48.07	28 tablets	£206.01
	10 mg	5 mg	£87.40	28 tablets	£46.82
	10 mg	20 mg	£87.40	28 tablets	£187.29
	15 mg	5 mg	£131.10	28 tablets	£46.82
	15 mg	20 mg	£131.10	28 tablets	£187.29
	20 mg	5 mg	£174.79	28 tablets	£46.82
	20 mg	20 mg	£174.79	28 tablets	£187.28
Quetiapine					
Tablet	25 mg	300 mg	£1.70	60 tablets	£10.20

	25 mg	800 mg	£1.70	60 tablets	£27.20
	100 mg	300 mg	£3.46	60 tablets	£5.19
	100 mg	800 mg	£3.46	60 tablets	£13.84
	150 mg	300 mg	£4.45	60 tablets	£4.45
	150 mg	800 mg	£4.45	60 tablets	£11.87
	200 mg	300 mg	£5.68	60 tablets	£4.26
	200 mg	800 mg	£5.68	60 tablets	£11.36
	300 mg	300 mg	£6.66	60 tablets	£3.33
	300 mg	800 mg	£6.66	60 tablets	£8.88
Modified-release tablet*	50 mg	50 mg	£67.66	60 tablets	£33.83
	50 mg	300 mg	£67.66	60 tablets	£202.98
	150 mg	50 mg	£113.10	60 tablets	£18.85
	150 mg	300 mg	£113.10	60 tablets	£113.10
	300 mg	50 mg	£170.00	60 tablets	£14.17
	300 mg	300 mg	£170.00	60 tablets	£85.00
	400 mg	50 mg	£226.20	60 tablets	£14.14
	400 mg	300 mg	£226.20	60 tablets	£84.83
Oral suspension*	20 mg/ml	300 mg	£95.00	150 ml	£285.00
	20 mg/ml	800 mg	£95.00	150 ml	£760.00
Risperidone					
Tablet	500 µg	1 mg	£2.76	20 tablets	£8.28
	500 µg	4 mg	£2.76	20 tablets	£33.12
	1 mg	1 mg	£4.02	20 tablets	£6.03
	1 mg	4 mg	£4.02	20 tablets	£24.12
	2 mg	1 mg	£21.55	60 tablets	£5.39
	2 mg	4 mg	£21.55	60 tablets	£21.55

	3 mg	1 mg	£26.86	60 tablets	£4.48
	3 mg	4 mg	£26.86	60 tablets	£17.91
	4 mg	1 mg	£32.74	60 tablets	£4.09
	4 mg	4 mg	£32.74	60 tablets	£16.37
	6 mg	1 mg	£43.58	28 tablets	£7.78
	6 mg	4 mg	£43.58	28 tablets	£31.13
Orodispersible tablet*	500 µg	1 mg	£14.79	28 tablets	£31.69
	500 µg	4 mg	£14.79	28 tablets	£126.77
	1 mg	1 mg	£21.66	28 tablets	£23.21
	1 mg	4 mg	£21.66	28 tablets	£92.83
	2 mg	1 mg	£39.59	28 tablets	£21.21
	2 mg	4 mg	£39.59	28 tablets	£84.84
	3 mg	1 mg	£43.50	28 tablets	£15.54
	3 mg	4 mg	£43.50	28 tablets	£62.14
	4 mg	1 mg	£50.27	28 tablets	£13.47
	4 mg	4 mg	£50.27	28 tablets	£53.86
Oral solution*	1 mg/ml	1 mg	£3.43	100 ml	£1.03
	1 mg/ml	4 mg	£3.43	100 ml	£4.12

* Costs used in the sensitivity analysis.
mg – milligram; ml – millilitre; µg – microgram.
The costs calculated based on (BNF, 2019).

Proton pump inhibitors

Proton pump inhibitors (PPI) are used to treat gastric and duodenal ulcers and in combination with antibacterials to treat Helicobacter pylori infection. After treatment for bleeding resulting from severe peptic ulcer, a high dose of PPIs (delivered into the vein) is used to reduce the risk of re-bleeding and surgery. PPIs are also used to treat dyspepsia, gastro-oesophageal reflux disease and ulcers associated with NSAID use. For patients with cystic fibrosis, PPIs are used to reduce the degradation of pancreatic enzyme supplements. High doses of PPIs may be required to control

excessive secretion of gastric acid in patients with Zollinger–Ellison syndrome (BNF, 2019).

PPIs are activated by acids and convert to sulfenic acids or sulfenamides. They react covalently with cysteines from the luminal surface of the ATPase. The covalent binding makes the inhibitory effects last longer than their plasma half-life (Shin & Sachs, 2008).

STOPP/START criteria

F2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > eight weeks (dose reduction or earlier discontinuation indicated).

(O'Mahony *et al*., 2015)

Proton pump inhibitors used in the analysis:

- Esomeprazole;
- Lansoprazole;
- Omeprazole;
- Pantoprazole;
- Rabeprazole.

Increased mortality

A series of articles published by Xie *et al*. looked at the mortality risk among proton pump inhibitor users. The authors conducted a longitudinal observational cohort study with a primary cohort of 349,312 patients, of which 275,977 patients were new PPI users and 73,335 were H2 blockers users. Another analysis looked at 3,288,092 patients comparing outcomes for PPI users vs people not using PPIs. Analysis was also conducted for a cohort of 2,887,030 patients, in which PPI users were compared with people not using PPIs and not using H2 blockers. The authors concluded there is an increased mortality risk among PPI users and the risk increases with prolonged use of PPIs. The table below presents the hazard ratio of increased risk of death related to the prolonged use of PPIs (Xie *et al*., 2017, 2019).

Table 6.9 The increased risk of mortality based on the duration of exposure to PPIs

PPI prescription in days	Hazard ratio mortality	Hazard ratio mortality (lower 95%CI)	Hazard ratio mortality (upper 95%CI)
31-90	1.05	1.02	1.08
91-180	1.17	1.13	1.20
181-360	1.31	1.27	1.34
361-720	1.56	1.47	1.51

PPI, Proton pump inhibitors, CI, Confidence Interval;
Controlled for gender, age, race, hospitalisations, eGFR, diabetes, hepatitis C, dementia, peripheral artery, HIV, cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, Helicobacter pylori, hypertension serum creatinine, achalasia, gastro-oesophageal reflux disease, bleeding, ulcers, Barrett's oesophagus, adenocarcinoma
Source: (Xie *et al*., 2017)

The hazard ratios are applied in the model in line with the cycle length and time horizon, based on the length of time the different hazard ratios are applied to the transition probability in line with the length of time that patients have been on proton pump inhibitors.

Cost of PPIs in the UK NHS

The cost of PPIs was based on the five medicines in the BNF. The average cost of these medicines is ($\bar{x}$ = £5.61; SE = 1.36), with the cost of the medicines presented in table 6.10.

Table 6.10 The costs of different PPI medicines available in the UK NHS

Dosage forms	Medicine concentration per unit	Standard daily dose	Drug tariff	Number of units	Monthly cost
Esomeprazole					
Gastro-resistant tablet	20 mg	20 mg	£2.15	28 tablets	£2.30
	40 mg	20 mg	£2.83	28 tablets	£1.52
Gastro-resistant capsule	20 mg	20 mg	£1.86	28 capsules	£1.99
	40 mg	20 mg	£2.27	28 capsules	£1.22

Gastro-resistant granules*	10 mg	20 mg	£25.19	28 sachets	£53.98
Powder for solution for injection*	40 mg	20 mg	£3.07	1 vial	£46.05
	40 mg	20 mg	£3.13	1 vial	£46.95
	40 mg	20 mg	£4.25	1 vial	£63.75
Lansoprazole					
Orodispersible tablet	15 mg	30 mg	£2.90	28 tablets	£6.21
	30 mg	30 mg	£4.26	28 tablets	£4.56
Gastro-resistant capsule	15 mg	30 mg	£0.76	28 tablets	£1.63
	30 mg	30 mg	£1.01	28 tablets	£1.08
Omeprazole					
Gastro-resistant tablet	10 mg	20 mg	£9.30	28 tablets	£19.93
	10 mg	20 mg	£7.90	28 tablets	£16.93
	20 mg	20 mg	£13.92	28 tablets	£14.91
	20 mg	20 mg	£5.97	28 tablets	£6.40
	40 mg	20 mg	£6.96	7 tablets	£14.91
	40 mg	20 mg	£6.17	7 tablets	£13.22
Gastro-resistant capsule	10 mg	20 mg	£0.82	28 capsules	£1.76
	20 mg	20 mg	£0.83	28 capsules	£0.89
	40 mg	20 mg	£0.62	7 capsules	£1.33
Powder for solution for infusion*	40 mg	60 mg	£26.00	5 vials	£234.00
Pantoprazole					
Gastro-resistant tablet	20 mg	40 mg	£0.90	28 tablets	£1.93
	40 mg	40 mg	£1.06	28 tablets	£1.14
Powder for solution for injection*	40 mg	40 mg	£5.00	1 vial	£150.00
	40 mg	40 mg	£22.50	5 vials	£135.00

Rabeprazole sodium					
Gastro-resistant tablet	10 mg	20 mg	£1.11	28 tablets	£2.38
	20 mg	20 mg	£1.46	28 tablets	£1.56

* Costs used in the sensitivity analysis
mg – milligram
The costs calculated based on (BNF, 2019)

Thiazide diuretics

Thiazide diuretics are prescribed to relieve oedema due to chronic heart failure and are indicated for reducing blood pressure.

Thiazide diuretics block the sodium-chloride channel in the proximal segment of the distal convoluted tubule. This leads to a lower level of sodium crossing the luminal membrane and in effect a decreased action of sodium-potassium pump. Therefore, there is less sodium and water passage to the interstitium (Akbari & Khorasani-Zadeh, 2019; BNF, 2019).

STOPP/START criteria

B8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatremia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatremia, hypercalcaemia and gout can be precipitated by thiazide diuretic).

(O'Mahony *et al*., 2015)

Thiazide diuretics used in the analysis:

- Bendroflumethiazide
- Chlorthalidone
- Indapamide
- Xipamide

Increased mortality

A study conducted on 1,163 HF patients, with a mean follow-up of 19.3 months, indicated a statistically significant increase in mortality risk for thiazide diuretic users. The authors conducted a propensity matching for patients treated with thiazide diuretics, given the significance of thiazide diuretics use and its association with long-term outcomes. Propensity matching was conducted for 206 patients; 103 thiazide diuretics users were matched with 103 patients not using thiazide diuretics. The difference for covariates was ≤ 10% after the score matching. In the thiazide diuretic group around 50% of patients died (51 deaths) and in the non-thiazide diuretic group around 27% of individuals died (28 deaths). Using the Cox proportional hazard regression model stratified for 206 matched patients, the hazard ratio was HR = 2.46 (95% CI; 1.29–4.69, p = 0.006). The hazard ratio was larger for the whole sample size, not just the matched patients, with hazard ratios ranging from 2.52 to 3.32 (depending whether the data were adjusted for different characteristics of the population) (Yamazoe *et al*., 2018).

Increased hospitalisation

The study also found a statistically significant difference in the adjusted means of sodium change for diuretic groups. Out of 1,001 patient that had normonatraemia at admission, 92 patients developed a hospital-acquired hyponatremia. After adjusting for covariates (such as age, gender, systolic blood pressure, brain natriuretic peptide, haemoglobin, glomerular filtration rate, left ventricular ejection fraction, use of diuretics and baseline sodium level), diuretic use was independently associated with hospital-acquired hyponatremia. The increased risk of developing hospital-acquired hyponatremia was statistically significant for patients on thiazide diuretics compared to loop diuretics, with an odds ratio of OR 2.67 (95%CI; 1.13–6.34) and OR 2.31 (95%CI 1.50–5.13) for low- and high-dose loop diuretics, respectively (Yamazoe *et al*., 2018).

Cost of thiazide diuretics in the UK NHS

Table 6.11 presents the costs of thiazide diuretics in the UK NHS. The average cost was $\bar{x}$ = £12.26; SE = 9.51. Because of the variation in the cost between different types of thiazide diuretics, there is high uncertainty associated with the value of this

parameter. However, this uncertainty was tested in sensitivity analysis, where extreme values for cost of thiazide diuretics were used.

Table 6.11 The costs of different thiazide diuretics available in the UK NHS

Dosage forms	Medicine concentration per unit	Standard daily dose	Drug tariff	Number of units	Monthly cost
Bendroflumethiazide					
Tablet	2.5 mg	5 mg	£0.54	28 tablets	£1.16
	2.5 mg	10 mg	£0.54	28 tablets	£2.31
	5 mg	5 mg	£0.60	28 tablets	£0.64
	5 mg	10 mg	£0.60	28 tablets	£1.29
Chlortalidone					
Tablet	50 mg	50 mg	£88.04	30 tablets	£88.04
Indapamide					
Tablet	2.5 mg	2.5 mg	£0.93	28 tablets	£1.00
Modified-release tablet	1.5 mg	1.5 mg	£3.40	30 tablets	£3.40
Xipamide					
Tablet	20 mg	20 mg	£19.46	140 tablets	£4.17
	20 mg	40 mg	£19.46	140 tablets	£8.34

* Costs used in the sensitivity analysis.
mg – milligram.
Costs calculated based on (BNF, 2019).

Benzodiazepines

The BNF provides two indications for the use of benzodiazepines:

1. severe, disabling or unacceptable by the patient anxiety. The anxiety can occur alone or with concurrent insomnia, psychosomatic, organic, or psychotic illness
2. insomnia, but only when severe, disabling or causing severe distress (BNF, 2019).

Benzodiazepines act on benzodiazepine receptors in the central nervous system, which allows the entrance of chloride ions into the neuron. The neuron is hyperpolarised by the addition of chloride anion, which leads to decreased firing of action potentials of that neuron (Bounds & Nelson, 2019).

STOPP/START criteria

K1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).

(O'Mahony *et al*., 2015)

Increased hospitalisation

A systematic literature review of falls in patients with HF identified benzodiazepines as a risk factor. The evidence is based on a retrospective case-control study of 200 patients, 100 patients who had fallen and 100 control patients. In the falls group, 40 patients had been using benzodiazepines, whereas in the control group it was 20 patients. This translates to an odds ratio of 2.67 (95%CI; 1.42-5.02) for patients on benzodiazepines having a greater risk of falling (Lee, Pressler & Titler, 2016).

Increased mortality

For increased risk of mortality following a major fall, please see section 6.3.4 'Input parameter 4: Adverse events of potentially inappropriate prescribing – Falls'.

Cost of benzodiazepines in the UK NHS

Table 6.12 presents the costs to the UK NHS of benzodiazepines. The average cost of seven different types of medicines was $\bar{x}$ = £14.43; SE = 6.07.

Table 6.12 The costs of different benzodiazepines medicines available in the UK NHS

Dosage forms	Medicine concentration per unit	Standard daily dose	Drug tariff	Number of units	Monthly cost
Flurazepam					
Capsule	15 mg	15 mg	£6.73	30 capsules	£6.73
	30 mg	15 mg	£8.63	30 capsules	£4.32
Temazepam					
Tablet	10 mg	10 mg	£2.97	28 tablets	£3.18
	20 mg	10 mg	£1.56	28 tablets	£0.84
Oral solution*	10 mg/5 ml	10 mg	£183.25	300 ml	£91.63
Diazepam					
Tablet	2 mg	2 mg	£0.59	28 tablets	£0.63
	2 mg	15 mg	£0.59	28 tablets	£4.74
	5 mg	2 mg	£0.61	28 tablets	£0.26
	5 mg	15 mg	£0.61	28 tablets	£1.96
	10 mg	2 mg	£0.66	28 tablets	£0.14
	10mg	15 mg	£0.66	28 tablets	£1.06
Oral suspension*	2 mg/5 ml	2 mg	£31.75	100 ml	£47.63
	2 mg/5 ml	15 mg	£31.75	100 ml	£357.19
Oral solution*	2 mg/5 ml	2 mg	£42.81	100 ml	£64.22
	2 mg/5 ml	15 mg	£42.81	100 ml	£481.61
Solution for injection*	10 mg/2 ml	10 mg	£5.50	10 ampoules	£16.50
	10 mg/2 ml	20 mg	£5.50	10 ampoules	£33.00
Enema*	2.5 mg	10 mg	£5.65	5 tubes	£135.60
	5 mg	10 mg	£5.85	5 tubes	£70.20
	10 mg	10 mg	£7.35	5 tubes	£44.10

Lorazepam					
Tablet	1 mg	1 mg	£3.07	28 tablets	£3.29
	1 mg	4 mg	£3.07	28 tablets	£13.16
	2.5 mg	1 mg	£7.26	28 tablets	£3.11
	2.5 mg	4 mg	£7.26	28 tablets	£12.45
Oral solution*	1 mg/ml	1 mg	£103.62	150 ml	£20.72
	1 mg/ml	4 mg	£103.62	150 ml	£82.90
Alprazolam					
Tablet	0.25 mg	0.5 mg	£3.18	60 tablets	£3.18
	0.25 mg/ml	0.75 mg	£3.18	60 tablets	£4.77
	0.5 mg	0.5 mg	£6.09	60 tablets	£3.05
	0.5 mg/ml	0.75 mg	£6.09	60 tablets	£4.57
Chlordiazepoxide hydrochloride					
Capsule	5 mg	15 mg	£11.50	100 capsules	£10.35
	10 mg	15 mg	£17.80	100 capsules	£8.01
Clonazepam					
Tablet	0.5 mg	4	£28.31	100 tablets	£67.94
	0.5 mg	8	£28.31	100 tablets	£135.89
	2 mg	4	£29.23	100 tablets	£17.54
	2 mg	8	£29.23	100 tablets	£35.08
Oral solution*	0.5 mg/5 ml	4	£76.94	150 ml	£0.62
	0.5 mg/5 ml	8	£76.94	150 ml	£1.23
	2 mg/5 ml	4	£108.36	150 ml	£0.22
	2 mg/5 ml	8	£108.36	150 ml	£0.43

* Costs used in the sensitivity analysis; ml – millilitre; mg – milligram
Costs calculated based on (BNF, 2019).

Any duplicate drug class prescription

Prescribing medicines from the same therapeutic group may be caused by: error of initiation of multiple medicines on the same day; lack of integrated care of patient by multiple providers; therapeutic augmentation or prescriptions of medications on an as-needed basis, for example for agitation or sleep impairment (Martin *et al*., 2009). There are also examples when duplication drug class prescription is appropriate, for example in some patients treated for diabetes.

The STOPP/START criterion for this PIP is: “Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent)” (O’Mahony *et al*., 2015).

Prescribing medicines from the same drug class may increase the risk of ADE. The STOPP/START criteria provide some evidence about the negative consequences of duplicate drug class prescription for a few populations, none of which are patients with HF. The negative consequences mentioned in the studies relate to issues with adherence to treatment (Martin *et al*., 2009) and ADE such as cognitive disturbances, hangover and falling (Olsson *et al*., 2010).

There was not enough evidence to allow for modelling the impact of duplicate drug class prescription on hospitalisation and mortality. The evidence that did exist was also related to a population other than patients with HF.

Hence, a conservative assumption was made that there was no increase in hospitalisation or mortality resulting from the duplication. The model only incorporates the additional cost of potentially inappropriate medicines. The monthly cost of duplication was assumed to be an average cost of all the PIPs included in the analysis ($\bar{x}$ = £20.94; SE = 2.60).

6.3.4 Input parameter 4: Adverse events of potentially inappropriate prescribing

Stable heart failure

Depending on whether the patient is still on PIP or not after discharge from hospital, they can be in one of two Markov states – PIP or no PIP. In both Markov states it is

assumed that the patients have stable heart failure and therefore the utility values assigned to these states are conservatively assumed to be the same. The stable HF utility comes from a study that rated the utilities for chronic HF in a time trade-off valuation study with a general population in Edinburgh and London. One-year health states were drafted for acute impact and post-acute event and health states data were collected to represent subsequent chronic state. Every participant rated both the acute and chronic states. For the chronic state the mean utility was 0.57 (SD = 0.32). This value was also used in a recent economic evaluation conducted by (Cowie, Simon, Klein & Thokala, 2017). Alternative utilities for stable heart failure were tested in the PSA and found to equal 0.8 (Göhler *et al*., 2009) and range between 0.46 and 0.82 (Griffiths *et al*., 2014) depending on the severity of HF (as per NYHA classification).

The disutility applied to the patients in PIP or no PIP state was 0.008 per year. This is taken from a Swedish longitudinal study that looked at 5,334 HF patients using the EQ-5D questionnaire (Berg *et al*., 2015). The same value was applied in two recent UK studies (Cowie *et al*., 2017; NICE, 2016).

The cost in the PIP and no PIP Markov states differed only by the cost of medications, where the cost for specific PIPs or the cost of alternative appropriate medicines was applied. However, the two Markov states had the same component of the cost which was a monthly cost of delivering treatment for patients with stable HF, on average £36 (Griffiths *et al*., 2014; Cowie *et al*., 2017).

Exacerbation of heart failure

Acute exacerbation of heart failure is a: “rapid onset or worsening of symptoms and/or signs of heart failure, requiring urgent evaluation and treatment”. The initial treatment involves the use of diuretics and oxygen. Pressor support or mechanical ventilation may be required for cardiogenic shock and early revascularisation for patients with acute myocardial infarction (Yusuf, 2018).

Cost of exacerbation of heart failure

To estimate the cost of hospitalisation for exacerbation of heart failure, I used the National Schedule of Reference Costs Year: 2017-18 (refer to chapter 4 for more

information about reference costs and how they are calculated). These reference costs were used to calculate the weighted average of HF admissions.

The reference cost provides five healthcare resource groups (HRG) that refer to patients with HF. These groups are:

- EB03A Heart Failure or Shock, with CC Score 14+
- EB03B Heart Failure or Shock, with CC Score 11-13
- EB03C Heart Failure or Shock, with CC Score 8-10
- EB03D Heart Failure or Shock, with CC Score 4-7
- EB03E Heart Failure or Shock, with CC Score 0-3

The total cost for the NHS of these five HRGs in the year 2017/18 was £331,986,721 with the total activity (the number of attendances in hospital) equalling 167,695. Therefore, in this cost-utility analysis I assumed the unit cost per hospitalisation in the analysis was £1,979.71. For the estimation of the standard error for sensitivity analysis, I used the formula mentioned in chapter 4 (please see the formula 6.3).

$$SE \approx \frac{Q3 - Q1}{(Z_{0.75} - Z_{0.25})\sqrt{n_t}} \quad (6.3)$$

SE – standard error
Q3 – third/upper quartile
Q1 – first/lower quartile
nt – number of NHS organisations on which the unit cost is based on
Z0.75 - Z Score of 0.75
Z0.25 - Z Score of 0.25

(Snowsill, 2016)

Health state utilities for exacerbation of heart failure

Disutility of -0.1 for each hospitalisation due to exacerbation of heart failure was applied. The same estimate was used in three recent cost-effectiveness analyses of health technologies in patients with HF as outlined below.

- the cost-utility analysis of a healthcare intervention of real-time pulmonary artery pressure monitoring for patients with HF (Cowie *et al*., 2017)
- heath-technology appraisal published by NICE of sacubitril valsartan for patients with HF (NICE, 2016)
- the cost-utility of ivabradine in the treatment of chronic HF (Griffiths *et al*., 2014).

Falls

Falls are a leading cause of morbidity, hospitalisation and mortality for older, frail people. Common reasons for older people falling are poorer physiology and physical functioning as well as comorbidity with related polypharmacy. Polypharmacy increases the risk of prescribing potentially inappropriate medications which lead to falls (Hartikainen, Lönnroos & Louhivuori, 2007; Hill & Wee, 2012; Huang *et al*., 2012). Some of the medicines that increase the risk of falls may be needed at the time of diagnosis, however they must be monitored and regularly reviewed, because they can cause more harm than benefit (Marvin *et al*., 2017).

There are many risk factors for falls:

- polypharmacy and potentially inappropriate prescribing
- previous history of falls
- urinary incontinence
- limitations of mobility like gait, instability or weakness of the lower limbs
- cognitive impairment
- dizziness
- confusion
- postural hypotension

(Dionyssiotis, 2012; Huang *et al*., 2012; Lee *et al*., 2016; NICE, 2013a)

The risk of an individual falling increases with the number of risk factors they have. Patients experiencing these risk factors may restrict their normal activity because of a justified fear that they may fall (Lee *et al*., 2016).

As with other patients, those with HF can experience fall-related symptoms such as head injury, cognitive impairment or postural hypotension. HF patients are at greater risk of falling as many of the drugs they take have side effects which can contribute to falls. For example, medicines such as digoxin, diuretics and type IA antidysrhythmics can all lead to patients falling (Lee *et al*., 2016).

<u>Type of falls</u>

Falls can differ in severity. For the purpose of economic modelling, I used the adapted version of the types of falls used by (Poole, Smith & Davies, 2015) in a

cost-effectiveness analysis of vitamin D in the prevention of falls. They describe three fall categories: minor falls, major falls and major falls which require long-term care. Table 6.13 presents the probabilities of the type of fall a patient may experience. The probabilities were used to determine the average cost of a single fall and the average utility value in the Markov model.

Table 6.13 Probabilities of different age groups of patients experiencing different types of fall (by severity)

Model parameter	Age bands			
	60–64	65–69	70–74	≥75
Minor fall	0.89	0.83	0.76	0.61
Major fall	0.11	0.17	0.22	0.28
Major fall which requires long-term care	0.00	0.00	0.02	0.11

Source: Adapted from (Poole *et al*., 2015).

Cost of falls

The potential costs of falls were sourced from the (Poole *et al*., 2015) study, which adapted the costs from (Scuffham, Chaplin & Legood, 2003). The authors collected inpatient costs from HES data and segregated them by appropriate age groups and type of falls using the ICD-10 codes (W01, W05, W06, W07, W08, W09, W10, W18, W19). The costs were derived by multiplying the health-related grouping (HRG) from HES data by the mean reference cost. Table 6.14 presents the summary of costs for the three types of falls categories in the Poole study.

Table 6.14 Unit cost per one fall for the UK NHS

Age	Minor fall	Major fall (weighted HRG acute costs)	Long-term care (six months)
60–64	£442	£2,622	£16,388
65–69	£456	£2,766	
70–74	£466	£3,603	
≥75	£462	£3,537	

Source: (Poole *et al*., 2015)

Health state utilities for falls

The health state utilities for patients with falls were calculated by deduction of disutility, for each fall that the patient had, from the baseline utility of 0.57 for patients with stable heart failure. I calculated the disutility based on data published in Poole *et al*. (2015), where the disutilities related to severe fear of falling and post-acute care. Admission to hospital following a major fall had the same disutility as post-acute care for 10 days, which is the average length of stay for HRG R29.6, tendency to fall, not elsewhere classified. The disutilities were conservatively assumed to remain the same for all the age groups. Table 6.15 presents the disutilities for minor fall, major fall and major fall requiring long-term care.

Table 6.15 Disutility values for patients who have fallen

Type of fall	Disutility following a fall
Minor fall	-0.017
Major falls	-0.032
Long-term care	-0.194

Source: Adapted from (Poole *et al*., 2015)

Mortality following fall

Heart failure patients who experience falls have an increased mortality risk. The risk varies based on the type of fall experienced. The increased mortality was weighted depending on the probability of type of fall (table 6.13).

Table 6.16 presents the increased risk of mortality following a fall. The mortality risk for patients with minor falls was conservatively assumed to be the same as for patients who have not fallen. The patients with major falls had increased probability of dying between 0.002 for age 60–64 and 0.01 for ≥75-year olds (Poole *et al*., 2015; Scuffham *et al*., 2003). The increased mortality risk for patients in long-term care was based on data from 2,540 patients residing in long-term care facilities from 18 local authorities (Bebbington, Darton & Netten, 2000).

Table 6.16 Increased mortality risk following a fall

Age	Probability of death following major fall	Probability of death while in long-term care
60–64	0.002	-
65–69	0.004	-
70–74	0.007	0.206
≥75	0.01	0.206

Source: Adapted from (Bebbington *et al*., 2000; Poole *et al*., 2015; Scuffham *et al*., 2003)

Hyponatremia

The final adverse outcome of medicines used in the model is hyponatremia, which is low concentration of sodium in the blood. Hyponatremia can be defined as a serum sodium concentration below 136 mmol/L (Adrogué & Madias, 2000) and is the most common electrolyte disorder in patients admitted to hospital. Hyponatremia may cause neurological disorders and is a common cause of morbidity and mortality. The mortality rates for patients with hyponatremia vary and are estimated between 5% and 50% depending on the severity of the condition (Liamis, Milionis & Elisaf, 2008).

Hyponatremia in patients with HF is a predictor for adverse outcomes including prolonged morbidity and mortality and patients with HF have several risk factors which contribute to hyponatremia. This includes altered cardiovascular physiology leading to retention of sodium and water in the body through activation of the renin-angiotensin-aldosterone system (Filippatos & Elisaf, 2013).

Hyponatremia can also be caused by medication including diuretics. A study of 1,163 HF patients (mean age 72.6 years) found that thiazide diuretic use was associated with hospital-acquired hyponatremia and that mortality was also higher in the thiazide diuretics group compared to patients not taking thiazide diuretics (Yamazoe *et al*., 2018).

<u>Cost of hyponatremia</u>

A systematic literature review with meta-analysis of the cost of hyponatremia (Corona *et al*., 2016) found eight studies that looked at the difference in mean hospitalisation cost between patients suffering from hyponatremia, compared to

patients without hyponatremia. Unfortunately, none of the studies was conducted solely in the UK. Due to lack of sufficient evidence of the cost of hospitalisation of hyponatremia in the UK NHS, the average cost from the systematic literature review was used in the modelling. In the meta-analysis the mean hospitalisation cost was £1,565 (95%CI; £731-£2,398). Costs were originally reported in USD. The costs were converted using the exchange rate from January 2018 (1 USD = 0.7364 GBP) and adjusted for inflation (Corona *et al*., 2016).

Health state utilities for hyponatremia

The health state utilities were based on two clinical studies SALT-1 and SALT-2 (Study of Ascending Levels of Tolvaptan in Hyponatremia), with a total of 448 patients enrolled in the trials. The health state utilities were estimated based on a Short-Form (SF-12) questionnaire, which is a patient-reported survey of patient health. Later, in the cost-effectiveness analysis published by M. Y. Lee *et al*. (2014), the utilities were mapped to another patient-reported survey, the EQ-5D questionnaire (where health status is measured by five dimensions: self-care, mobility, pain/discomfort, anxiety/depression and usual activities) (Drummond *et al*., 2015). The utility weights represented different health states based on the sodium level. In the cost-effectiveness modelling of CMR the utility of 0.521 was used to represent marked hyponatremia, sodium level below 130mEq/L.

6.3.5 Summary of all input parameters

Parameters used in the decision tree model

Table 6.17 presents the summary of all parameters used in the decision tree model. The time horizon for the decision tree model was one month. The age of patients when they enter the model is 70, the cycle length is one month and the discount rate for both benefits and costs is 3.5%. The decision tree model includes the transition probabilities for patients having PIP in both the intervention and control groups. The probabilities of patients being on specific PIPs are the same for both the intervention and the control group. Other parameters include the odds ratio for improvement in PIP rates after CMR compared with usual care. Finally, the decision tree model includes the costs: a) of CMR, derived from the cost of pharmacist work multiplied by the time needed to complete the CMR and b) of medicines included in the model.

These parameters are also used in the Markov model when patients are readmitted to hospital.

Table 6.17 Parameters used for the decision tree model (base-case analysis)

Model parameter	Value of the parameter	Distribution	Source
Model assumptions			
Age	70	–	(Conrad *et al*., 2018; European Society of Cardiology, 2016; NCAP, 2018).
Time horizon	Lifetime (25 years)	–	–
Cycle length	One month	–	(Cowie *et al*., 2017; Griffiths *et al*., 2014; NICE, 2016)
Discount rate for benefits and costs	3.5%	–	(NICE, 2013b)
Costs			
Pharmacist cost	£45/h	Gamma	(Curtis & Burns, 2018)
Cost of CMR	£25.20 (SE = 0.03)	Gamma	(Brodersen Lind *et al*., 2016; Curtis & Burns, 2018)
Cost of medicines			
Proton pump inhibitors	£5.61 (SE = 1.36)	Gamma	(BNF, 2019)
Benzodiazepines	£14.43 (SE = 6.07)	Gamma	(BNF, 2019)
Any duplicate drug class prescription	£20.94 (SE = 2.60)	Gamma	(BNF, 2019)
Thiazide diuretics	£12.26 (SE = 9.51)	Gamma	(BNF, 2019)

Non-steroidal anti-inflammatory drugs	£19.10 (SE = 4.54)	Gamma	(BNF, 2019)
Neuroleptic drugs	£26.21 (SE = 0.65)	Gamma	(BNF, 2019)
Cost of medicines prescribed in place of PIPs	£21.35 (SE = 2.60)	Gamma	(BNF, 2019; Ward *et al*., 2019)
Probabilities			
Probability of patient being on PIP (CMR)	0.20	Beta	(Bermingham *et al*., 2014; Hill-Taylor *et al*., 2016)
Probability of patient being on PIP (usual care)	0.58 (SE = 0.02)	Beta	(Bermingham *et al*., 2014)
Probability of what PIP the patient would be on (both CMR and usual care)			
Proton pump inhibitor for peptic ulcer disease at full therapeutic dosage for >8 weeks	0.43 (SE = 0.04)	Beta	(Bermingham *et al*., 2014)
Benzodiazepines	0.34 (SE = 0.03)	Beta	(Bermingham *et al*., 2014)
Any duplicate drug class prescription	0.09 (SE = 0.02)	Beta	(Bermingham *et al*., 2014)
Thiazide diuretic with current significant gout	0.05 (SE = 0.02)	Beta	(Bermingham *et al*., 2014)
Non-steroidal anti-inflammatory drugs with heart failure	0.05 (SE = 0.01)	Beta	(Bermingham *et al*., 2014)
Neuroleptic drugs	0.05 (SE = 0.01)	Beta	(Bermingham *et al*., 2014)
Odds ratio			
Odds ratio for improvement in PIP rates after CMR compared with usual care	2.98 (95%CI 1.30; 6.83)	LogNormal	(Hill-Taylor *et al*., 2016)

BNF, British National Formulary; CMR, comprehensive medication review; CI, confidence interval; PIP, potentially inappropriate prescribing; SE, standard error

Parameters used in the Markov model

The Markov model uses the same parameters as the decision tree model: when patients are hospitalised or are on PIPs. The model was run for a lifetime horizon (the model ran for a total of 25 simulated years, where the survival for patients was close to 0). Additional parameters only used in the Markov model include the monthly cost for management of stable HF and the utility values for patients with stable HF. Other parameters used in the model are hospitalisation risk, mortality risk, cost of hospitalisation and disutility values for the three type of adverse drug events: exacerbation of HF, falls and hyponatremia (table 6.18).

Table 6.18 Parameters used for the Markov model (base-case analysis)

Model parameter	Value of the parameter	Distribution	Source
Costs			
Monthly cost of treatment of stable HF	£36	Gamma	(Cowie *et al*., 2017; Griffiths *et al*., 2014)
Cost of hospitalisation for exacerbation of HF	£1,980 (SE = 82.64)	Gamma	(Reference Cost, 2018)
Cost of hospitalisation for falls (patients 60–64 years old)	£684 (SE = 171.06)	Gamma	(Poole *et al*., 2015)
Cost of hospitalisation for falls (patients 65–69 years old)	£854 (SE = 213.57)	Gamma	(Poole *et al*., 2015)
Cost of hospitalisation for falls (patients 70–74 years old)	£1,497 (SE = 374.13)	Gamma	(Poole *et al*., 2015)
Cost of hospitalisation for falls (patients ≥75 years old)	£3,031 (SE = 757.76)	Gamma	(Poole *et al*., 2015)
Cost of hospitalisation for hyponatremia	£1,565* (SE = 405.22)	Gamma	(Corona *et al*., 2016)
Mortality risk (hazard ratios)			
Hazard ratio for increased mortality for HF	HR 2.46,	LogNormal	(Yamazoe *et al*., 2018)

patients on thiazide diuretics	(95% CI 1.29; 4.69)		
Hazard ratio for increased mortality for HF patients on NSAIDs	HR 1.49 (95% CI 1.22; 1.84)	LogNormal	(Gislason *et al*., 2009)
Increased mortality following exposure to PPI for:			
31–90 days	HR 1.05 (95% CI 1.02; 1.08)	LogNormal	(Xie *et al*., 2017)
91–180 days	HR 1.17 (95% CI 1.13; 1.20)	LogNormal	(Xie *et al*., 2017)
181–360 days	HR 1.31 (95% CI 1.27; 1.34)	LogNormal	(Xie *et al*., 2017)
361–720 days	HR 1.51 (95% CI 1.47; 1.56)	LogNormal	(Xie *et al*., 2017)
Probability of death following major fall			
60–64 years old	0.002	Beta	(Poole *et al*., 2015; Scuffham *et al*., 2003)
65–69 years old	0.004	Beta	(Poole *et al*., 2015; Scuffham *et al*., 2003)
70–74 years old	0.007	Beta	(Poole *et al*., 2015; Scuffham *et al*., 2003)
≥75 years old	0.01	Beta	(Poole *et al*., 2015; Scuffham *et al*., 2003)
Probability of death while in long-term care after a major fall			
≥ 70 years old	0.206	Beta	(Bebbington *et al*., 2000; Poole *et al*., 2015)
Hospitalisation risk			
HR for increased hospitalisation because of exacerbation of HF for patients on NSAIDs	HR 1.23 (95% CI 1.17; 1.31)	LogNormal	(Gislason *et al*., 2009)

OR for increased hospitalisation because of hyponatremia for HF patients on thiazide diuretics	OR 2.67 (95% CI 1.13; 6.34)	LogNormal	(Yamazoe *et al*., 2018)
OR for increased risk of falls for HF patients on benzodiazepines	OR 2.67 (95% CI 1.42; 5.02)	LogNormal	(Lee *et al*., 2016)
OR for increased risk of falls for patients on neuroleptic drugs	OR 1.39 (95% CI 0.94; 2.00)	LogNormal	(Hill & Wee, 2012)
Utilities			
Death	0	Fixed	(Drummond *et al*., 2015)
Utility value for patients with stable HF	0.57	Beta	(Matza *et al*., 2015)
Disutility for patients with stable HF per one year	-0.008	Beta	(Berg *et al*., 2015; Cowie *et al*., 2017)
Disutility after minor falls	-0.017	Beta	(Poole *et al*., 2015)
Disutility after major falls	-0.032	Beta	(Poole *et al*., 2015)
Disutility after major falls requiring long-term care	-0.194	Beta	(Poole *et al*., 2015)
Disutility for patients hospitalised for hyponatremia	-0.049	Beta	(Lee *et al*., 2014)
Disutility for hospitalisation because of exacerbation of HF	-0.100	Beta	(Cowie *et al*., 2017)

CMR, comprehensive medication review; CI, confidence interval; HF, heart failure; HR, hazard ratio; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PPI, Proton pump inhibitors; SE, standard error
*Costs were originally reported in USD. The costs were converted using the exchange rate from January 2018 (1 USD = 0.7364 GBP) and adjusted for inflation

Parameters used in the sensitivity analysis

As well as the conventional PSA based on distributions around the point estimate of the base-case parameters (tables 6.17 and 6.18), I also conducted PSA that included alternative parameters presented in table 6.19. The alternative parameters

are either the same parameters from different data sources (utilities or costs) or parameters which represent different assumptions in the model. A different assumption can be for example changing the prevalence of PIPs to represent the general population of patients instead of the prevalence of PIPs for patients with HF. Another assumption tested was the subgroup analysis for different groups of patients depending on the severity of HF measured by NYHA classification. For all these parameters and assumptions, a PSA using 10,000 second-order Monte Carlo simulations was conducted.

Table 6.19 Probabilistic sensitivity analysis parameters used for generating 10,000 second-order Monte Carlo simulations

Parameter	Mean value	Distribution	alpha	beta	Source
Prevalence of PIPs for general population					
Probability of patient being on PIP (CMR)	0.29	Beta	295,653	723,838	(Bradley *et al.*, 2014)
Probability of patients in the general population (both CMR and usual care) being on each PIP					
PPI for peptic ulcer disease for > 8 weeks	0.20	Beta	38,153	149,077	(Bradley *et al.*, 2014)
Benzodiazepines	0.10	Beta	18,415	168,815	(Bradley *et al.*, 2014)
Any duplicate drug class prescription	0.65	Beta	121,668	65,562	(Bradley *et al.*, 2014)
Thiazide diuretic with current significant gout	0.03	Beta	6,094	181,136	(Bradley *et al.*, 2014)
NSAID with heart failure	0.00	Beta	409	186,821	(Bradley *et al.*, 2014)
Neuroleptic drugs	0.01	Beta	2,491	184,739	(Bradley *et al.*, 2014)

Utilities					
Disutility after major falls	0.06	Gamma	22.13	368.79	(Moriarty, Cahir, Bennett & Fahey, 2019)
Disutility after major falls requiring long-term care	0.203	Gamma	209.33	1,031.2	(Moriarty *et al*., 2019)
Disutility for patients hospitalised for hyponatremia	−0.136	Beta	97.46	127.1057	(Lee *et al*., 2014)
Utility value for patients with stable HF					
Utility value for patients with stable HF	0.80	Beta	785.6318	196.4080	(Göhler *et al*., 2009)
NYHA I	0.82	Beta	235.5706	51.7106	(Griffiths *et al*., 2014)
NYHA II	0.74	Beta	277.3381	97.4431	(Griffiths *et al*., 2014)
NYHA III	0.64	Beta	287.3600	161.6400	(Griffiths *et al*., 2014)
NYHA IV	0.46	Beta	222.7119	261.4444	(Griffiths *et al*., 2014)
Disutility for hospitalisation for HF					
Disutility for hospitalisation because of exacerbation of HF	−0.105	Beta	513.67	590.9967	(NICE, 2016)

NYHA I	−0.04	Beta	594.10	167.5667	(Griffiths *et al*., 2014)
NYHA II	−0.07	Beta	657.72	323.9500	(Griffiths *et al*., 2014)
NYHA III	−0.10	Beta	595.62	507.3800	(Griffiths *et al*., 2014)
NYHA IV	− 0.29	Beta	106.44	519.6722	(Griffiths *et al*., 2014)
Costs					
Cost of hospitalisation for major fall	£2,467.98†	Gamma	25	0.009	(Moriarty *et al*., 2019)
Cost of long-term care after major fall	£15,428.89†	Gamma	385.34	0.022	(Moriarty *et al*., 2019)
Hyponatremia	£345.70*	Gamma	39.13	8.83	(Deitelzweig *et al*., 2013)
Exacerbation of HF	£2,038	Gamma	608.19	3.35	(Cowie *et al*., 2017)

CMR, comprehensive medication review; HF, heart failure; NSAIDs, non-steroidal anti-inflammatory drugs; NYHA, New York Heart Association; PIP, potentially inappropriate prescribing; PPI, Proton pump inhibitors

*Costs were originally reported in USD. The costs were converted using the exchange rate from January 2018 (1 USD = 0.7364 GBP) and adjusted for inflation

† Costs were originally reported in EUR. The costs were converted using the exchange rate from January 2018 (1 EUR = 0.8870 GBP) and adjusted for inflation

6.4 Results

6.4.1 Base–case analysis

In the base-case analysis the combined results from the decision tree and Markov modelling done over a lifetime horizon showed that the mean length of survival for heart failure patients who received CMR intervention was 5.17 years compared with 4.98 years for heart failure patients on usual care. Receiving CMR in hospital was predicted to improve patients' survival by two months and eight days compared with usual care. Quality-adjusted life years (QALYs) per patient for the CMR group was 2.40 and in the usual care group it was 2.32. This reflected an increase of 0.08 QALYs for the patients receiving CMR.

From the perspective of the UK NHS and PSS, the cost of hospitalised HF patients receiving CMR over a lifetime horizon would be £4,778.82 per patient compared to £4,534.31 per patient for the usual care group. The model estimated that the cost would be £244.51 higher per patient for the CMR group compared to the usual care group.

The incremental cost-effectiveness ratio (ICER) per additional QALY gained for CMR versus usual care was estimated to be £3,123/QALYs, well below both the £10,000 and £20,000-£30,000 thresholds.

6.4.2 Deterministic sensitivity analysis

Several sensitivity analyses were undertaken to test the firmness of the results from the base-case analysis. For the base-case analysis the assumptions and value of parameters were altered to reflect the uncertainties around reliability of data and model assumptions. The deterministic sensitivity analysis was done for the best- worst-case scenarios. Subsequently, more in-depth deterministic analysis was conducted for four parameters with the greatest uncertainty from the best- worst-case scenarios analysis.

Best- worst-case scenario

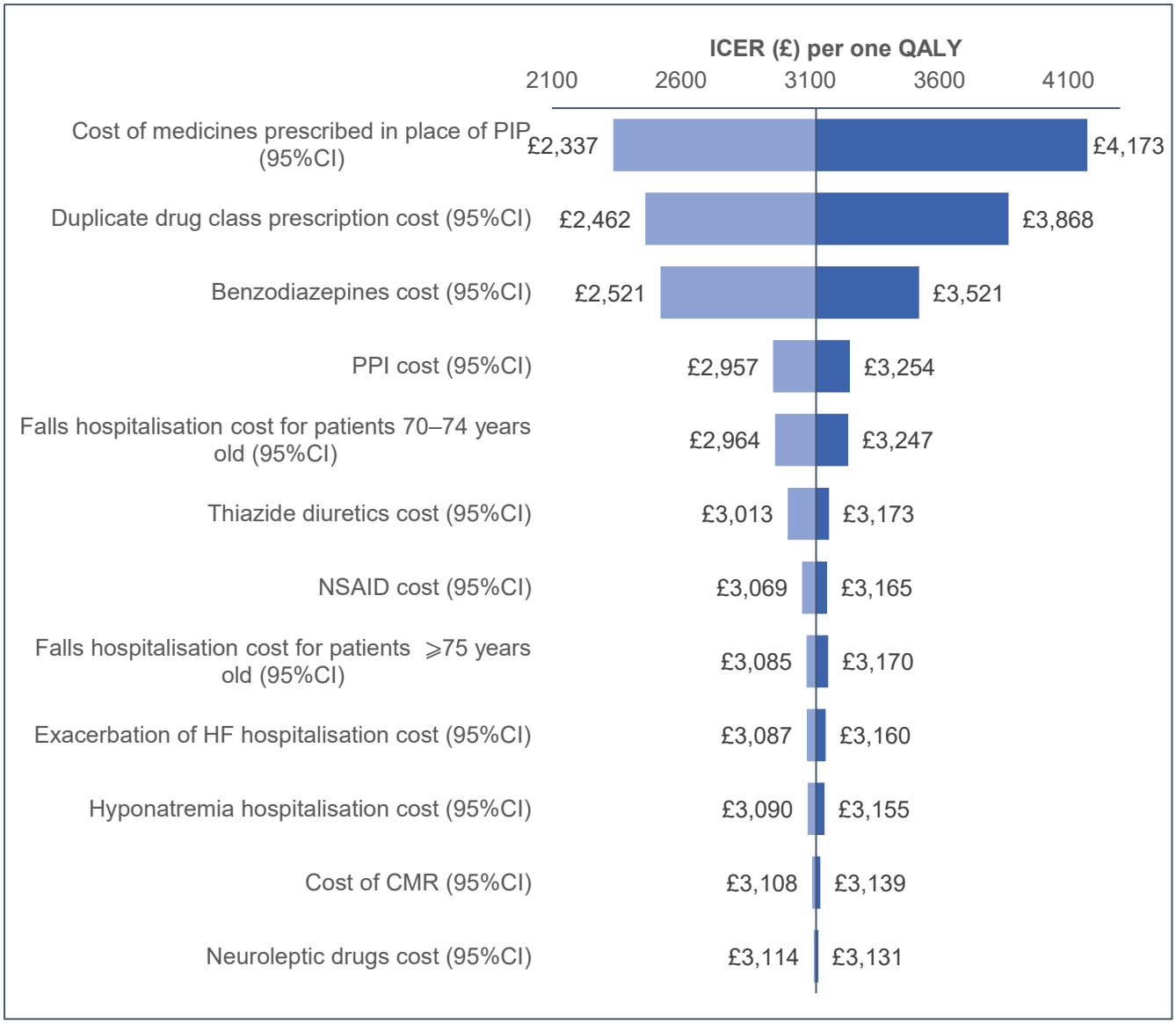
The best- and worst-case scenario analysis was conducted to test the results if one of the parameters in the model was altered to represent extreme values while the

rest remained at the base-case value. The results of the analysis are presented using tornado diagrams, where each parameter is represented by a horizontal bar that shows the variation in the ICER result around a central value (the base-case value of ICER). The horizontal bars with the biggest variation are on top of the diagram to represent that the model is most sensitive to this parameter.

The ICER remains below £20,000 in all scenarios, which means that the extreme values of the model do not change the general interpretation of the results and CMR was assumed to be cost-effective in all scenarios. In terms of cost parameters, the ICER was most sensitive to change in the cost of alternative medicines prescribed in place of PIP, where the ICER in the best-case scenario was at £2,337 per QALY and in the worst-case scenario at £4,173 per QALY (figure 6.5). The variation was also high for the cost of duplicate drug class prescription and the cost of benzodiazepines; the ICER per one QALY was £2,462 and £2,521 (respectively) for the best-case scenario and £3,868 and £3,521 (respectively) for the worst-case scenario.

Figure 6.5 Tornado diagram for cost data, best- worst-case analysis

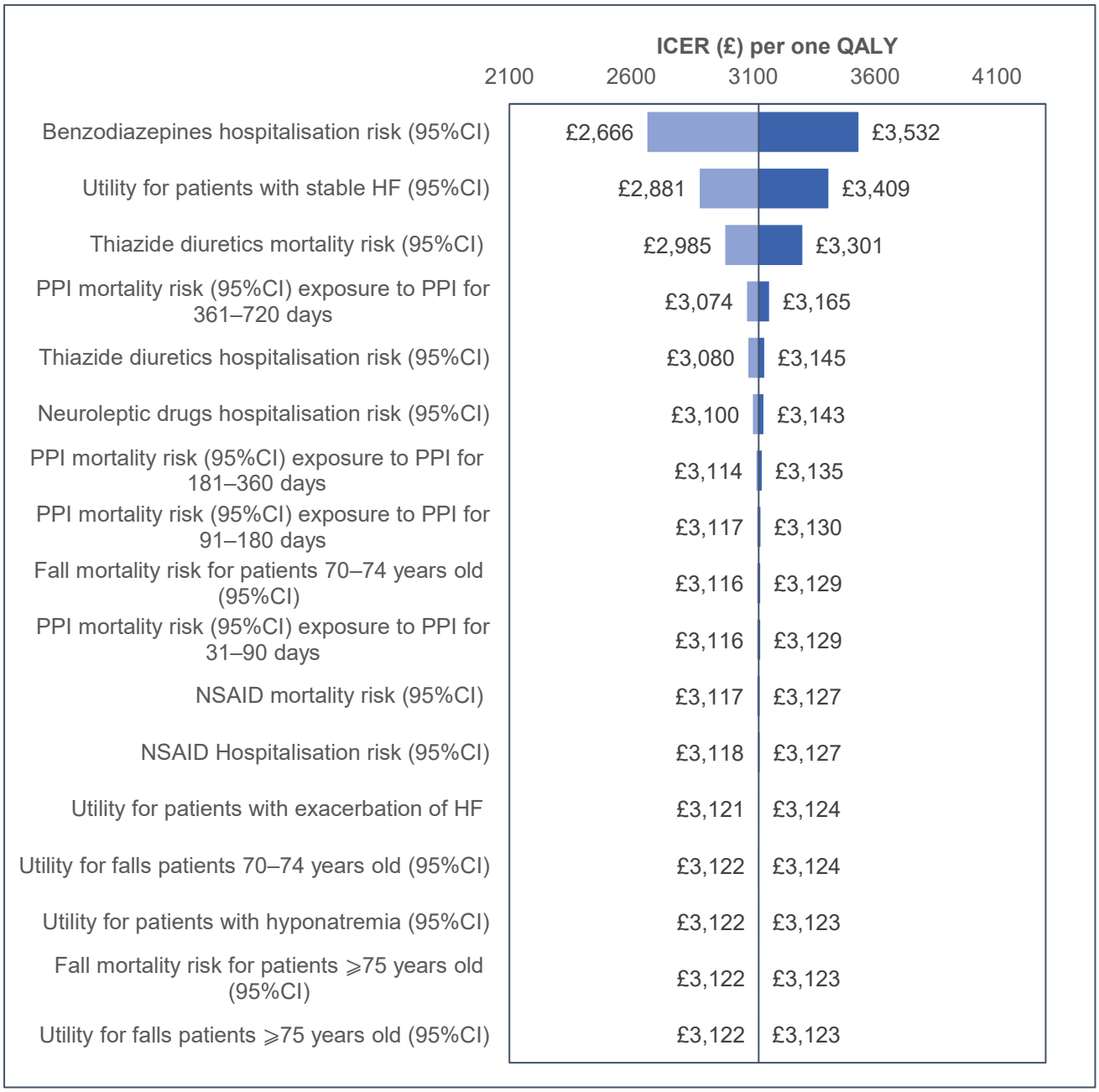
Base-case analysis ICER = £3,123 per one QALY



The best- worst-case analysis was also conducted for other parameters from the Markov model, where extreme values concerning benzodiazepines again had high variation, which means the model was sensitive to the value of that parameter. From figure 6.6 we can see that the value of ICER per QALY for the increased risk of hospitalisation for patients on benzodiazepines was £2,666 in the best-case and £3,532 in the worst-case scenario. Other parameters that had the highest variation were the value of utility parameter for patients with stable HF (best-case £2,881, worst-case £3,409) and the increased mortality risk for patients on thiazide diuretics (best-case £2,985, worst-case £3,301).

Figure 6.6 Tornado diagram for Markov model parameters, best- worst-case analysis

Base-case analysis ICER = £3,123 per one QALY

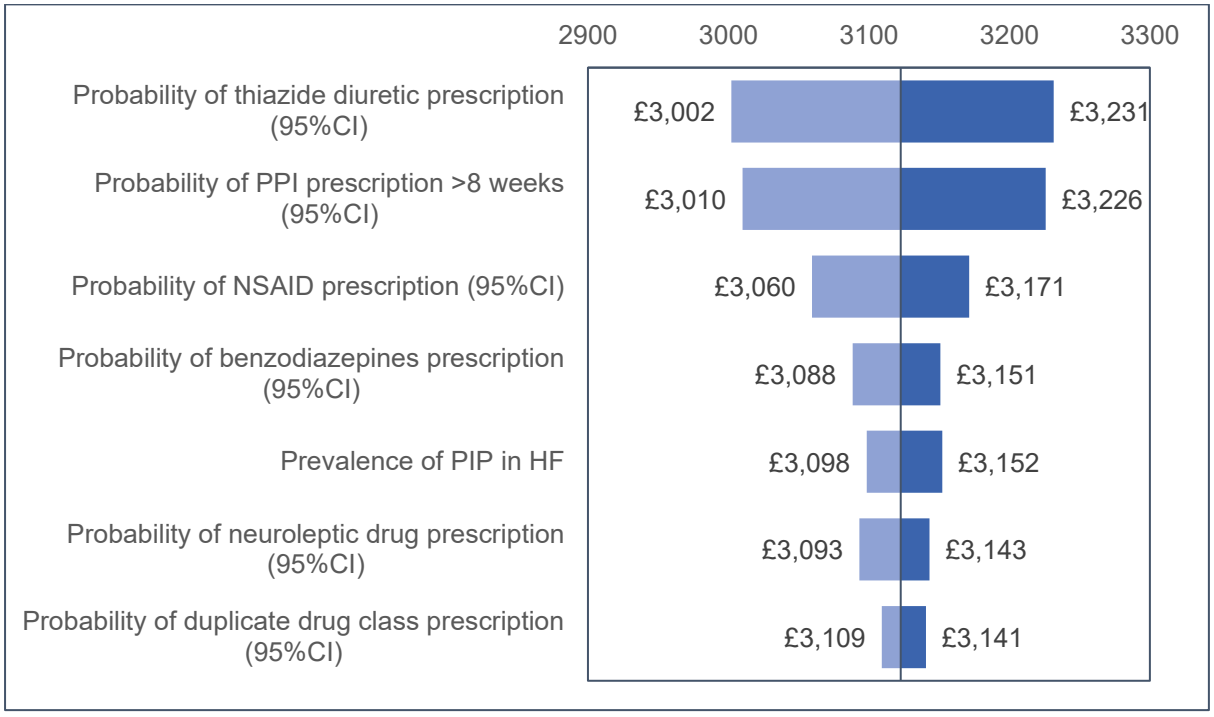


Finally, the extreme values for the parameters from the decision tree model were tested (figure 6.7). The highest variation was in the values of ICER for the probability of a patient being prescribed thiazide diuretic as a PIP, which ranged from £3,002 to £3,231 per QALY. Similar variation in the value of ICER was seen in the probability of PIP being proton pump inhibitor prescription > 8 weeks (best-case £3,010,

worst-case £3,226) and the probability of having PIP as NSAID prescription (best-case £3,060, worst-case £3,171).

Figure 6.7 Tornado diagram for decision tree model parameters, best- worst-case analysis

Base-case analysis ICER = £3, 123 per one QALY



The best- and worst-case analysis helped establish the parameters to which the model is most sensitive. Additional analyses were undertaken to test the most influential parameters which impact the cost-effectiveness of CMR based on the following parameters:

1. Effectiveness of CMR in reducing PIPs
2. Type of PIPs
3. The cost of substitute medicine prescribed instead of PIPs
4. Prevalence of PIPs

Parameter 1: Effectiveness of CMR in reducing PIPs

The effectiveness of CMR in reducing PIPs comes from a systematic literature review of randomised controlled trials that evaluated CMR using the STOPP/START criteria against usual care. Because the effectiveness of CMR can vary depending on the context in which it is delivered and the level of complexity of the intervention

(e.g. who carries out CMR, complexity of polypharmacy and severity of disease of the patient (see chapters 2 and 4 for more information)), a broad analysis of different levels of effectiveness of CMR was undertaken. To add additional analytical value of the sensitivity analysis the cost of one-off CMR intervention was modified to see at what cost of CMR and at what effectiveness the results of ICER change. Table 6.20 presents different values of ICER when two parameters were altered:

- The relative effectiveness of CMR in reducing PIP from 0% – no PIPs deprescribed, to 100% – all PIPs deprescribed.
- The cost of CMR – from £10 to £300 per one CMR intervention.

The results suggest that if CMR was not effective in reducing PIPs, then usual care would be the more cost-effective option. However, even 10% effectiveness of CMR suggests that CMR is cost-effective if the unit price of CMR is less than £93 for a £10,000 threshold and £223 for a threshold of £20,000.

Table 6.20 Two-way sensitivity analysis: alternating the cost and effectiveness of CMR (Base-case analysis ICER = £3,123 per one QALY)

		Unit price of CMR							
		£10	£20	£30	£40	£50	£100	£200	£300
Effectiveness of CMR described as the % of PIP deprescribed	0%	CMR dominated by UC							
	10%	£3,597	£4,367	£5,138	£5,908	£6,679	£10,531	£18,236	£25,941
	20%	£3,212	£3,598	£3,984	£4,369	£4,755	£6,684	£10,541	£14,399
	30%	£3,084	£3,341	£3,599	£3,856	£4,114	£5,401	£7,976	£10,551
	40%	£3,020	£3,213	£3,406	£3,600	£3,793	£4,760	£6,694	£8,628
	50%	£2,981	£3,136	£3,291	£3,446	£3,601	£4,375	£5,924	£7,473
	60%	£2,956	£3,085	£3,214	£3,343	£3,473	£4,119	£5,411	£6,704
	70%	£2,937	£3,048	£3,159	£3,270	£3,381	£3,936	£5,045	£6,154
	80%	£2,923	£3,021	£3,118	£3,215	£3,312	£3,798	£4,770	£5,742
	90%	£2,913	£2,999	£3,086	£3,172	£3,259	£3,691	£4,556	£5,421
	100%	£2,904	£2,982	£3,060	£3,138	£3,216	£3,606	£4,385	£5,165

CMR, comprehensive medication review; UC, usual care; PIP, potentially inappropriate prescribing. Red – not cost-effective or ICER > £20,000; yellow – cost-effective but ICER > £10,000; green – intervention offering exceptional value for money, with ICER <£10,000

Parameter 2: Type of potentially inappropriate prescription

To test the impact of each of the PIP medicines on the ICER, two scenarios were assumed in the sensitivity analysis. In scenario (a) each of the six PIPs included in the base-case analysis was excluded one at a time from the model in the sensitivity analysis. The probabilities of receiving this specific PIP were distributed proportionally among all the other five PIPs, as per data on the prevalence of specific PIPs in patients with HF (see subsection 'Prevalence of PIPs in target population' of section 6.1.3.1 for more details). In scenario (b) the assumption was to include only one of the six PIPs from the base-case analysis. For example, if a patient receives a PIP, then there is 100% probability that this PIP would be thiazide diuretic. The analysis was conducted for each of the six PIPs separately.

Scenario (a) – excluding any of the six PIPs from the analysis – did not result in changes to the cost-effectiveness of CMR. In all six scenarios CMR was a cost-effective option. CMR was most cost-effective in a scenario that did not include 'proton pump inhibitor for peptic ulcer disease at full therapeutic dosage for > 8 weeks', where the ICER was lowest at £2,118 per QALY. The least cost-effective option in the analysis was not considering PIP 'any duplicate drug class', in which the ICER was £3,239 – still well within the cost-effectiveness threshold of £20,000 (table 6.21).

Scenario (b) – the results changed for two of the six PIPs when the sensitivity analysis was conducted. When it was assumed that the only PIP in the analysis was 'any duplicate drug class' then CMR was no longer cost-effective, and it became a more expensive option with no QALY gain compared to usual care. The other result that changed was if we assume that the only PIP that patients receive are neuroleptics, which can lead to falls. In this assumption the CMR dominated over usual care, meaning that it was a less costly and more effective option. The biggest gain in QALYs resulted from receiving CMR for patients on thiazide diuretics, where the QALY gain was 0.3. It was also the most expensive option with an additional £662 that would need to be spent per patient (table 6.21).

Table 6.21 Sensitivity analysis based on types of potentially inappropriate prescription included in the analysis

STOPP criteria	Scenario (a) selected PIP excluded from the analysis			Scenario (b) only selected PIP included in the analysis		
	Incremental cost	QALY gain	ICER	Incremental cost	QALY gain	ICER
PPI	£111	0.05	£2,118	£422	0.11	£3,737
Benzodiazepines	£334	0.11	£3,153	£46	0.02	£2,044
Any duplicate drug class	£346	0.11	£3,239	£28	0.00	CMR dominated by UC
Thiazide diuretic	£265	0.09	£3,091	£662	0.30	£2,187
NSAIDs	£243	0.08	£3,215	£276	0.13	£2,052
Neuroleptics	£258	0.08	£3,160	-£38	0.01	CMR dominates over UC

QALY, quality-adjusted life year; STOPP, Screening Tool of Older Person's Prescriptions; ICER, incremental cost-effectiveness ratio; CMR, comprehensive medication review; UC, usual care; PIP, potentially inappropriate prescribing; PPI, proton pump inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs
Red – not cost-effective or ICER > £20,000; light green – intervention offering exceptional value for money, with ICER <£10,000; dark green – CMR dominates over usual care

Parameter 3: The cost of substitute medicine prescribed instead of PIPs

The monthly cost per patient of the appropriate medicines prescribed instead of PIPs was assumed to be £21.35. This figure was based on average cost of PIPs (from BNF) and the difference between the cost of PIPs and the cost of started alternatives (see section 6.1.3.3 'Cost and resources'). Because there is uncertainty surrounding this value, a deterministic sensitivity analysis was conducted in which the costs were adjusted to represent a variety of possible costs.

If the monthly cost of substitute medicines was assumed to be £0, which means no medicines were prescribed in place of PIPs, then CMR would dominate over usual care. On the other hand, if the substitute medicines were much more expensive than PIPs and monthly cost was equal to or above £134, then ICER was above £20,000, which would suggest that CMR would not be cost-effective. Table 6.22 summarises the results for different scenarios when the price of substitute medicines is altered.

Table 6.22 One-way sensitivity analysis: alternating the cost of the appropriate medicines prescribed instead of PIPs

	Monthly cost per patient of the appropriate medicines prescribed instead of PIPs						
	£0	**£10**	**£20**	**£30**	**£50**	**£100**	**£150**
Incremental cost	-£8	£110	£228	£347	£584	£1,175	£1,767
QALY gain	0.08						
ICER	CMR dominates over UC	£1,406	£2,918	£4,430	£7,453	£15,011	£22,569

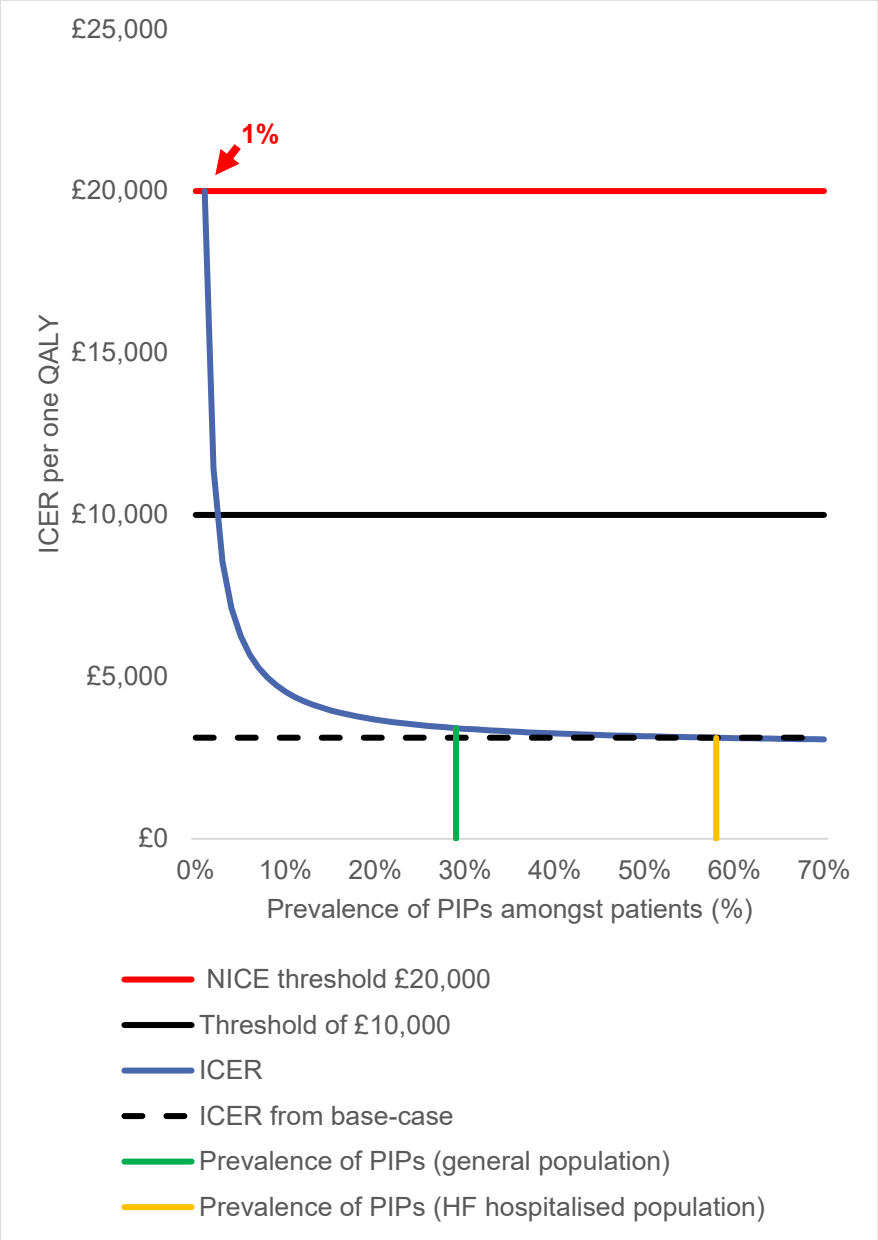
CMR, comprehensive medication review; ICER, incremental cost-effectiveness ratio; PIP, potentially inappropriate prescribing; QALY, quality-adjusted life year; UC, usual care
Red – not cost-effective or ICER > £20,000; yellow – cost-effective but ICER > £10,000; light green – intervention offering exceptional value for money, with ICER < £10,000; dark green – CMR dominates over usual care

Parameter 4: Prevalence of potentially inappropriate prescribing

As described in section 6.1.3 'Outcomes', there is uncertainty surrounding the prevalence of PIPs in the target population as the estimates of prevalence in the

literature vary significantly. In the sensitivity analysis I tested a broad range of different prevalence and plotted the results in figure 6.8. The results of the analysis suggest that if more than 1% of the population is receiving PIPs, then the CMR is cost-effective (below the £20,000 threshold). As described in chapter 5, the prevalence of PIPs for HF patients ranges from 15% to 58%.

Figure 6.8 Sensitivity analysis based on modifying the parameter: PIP prevalence



PIP, potentially inappropriate prescribing; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; HF, heart failure; NICE, The National Institute for Health and Care Excellence

6.4.3 Probabilistic sensitivity analysis

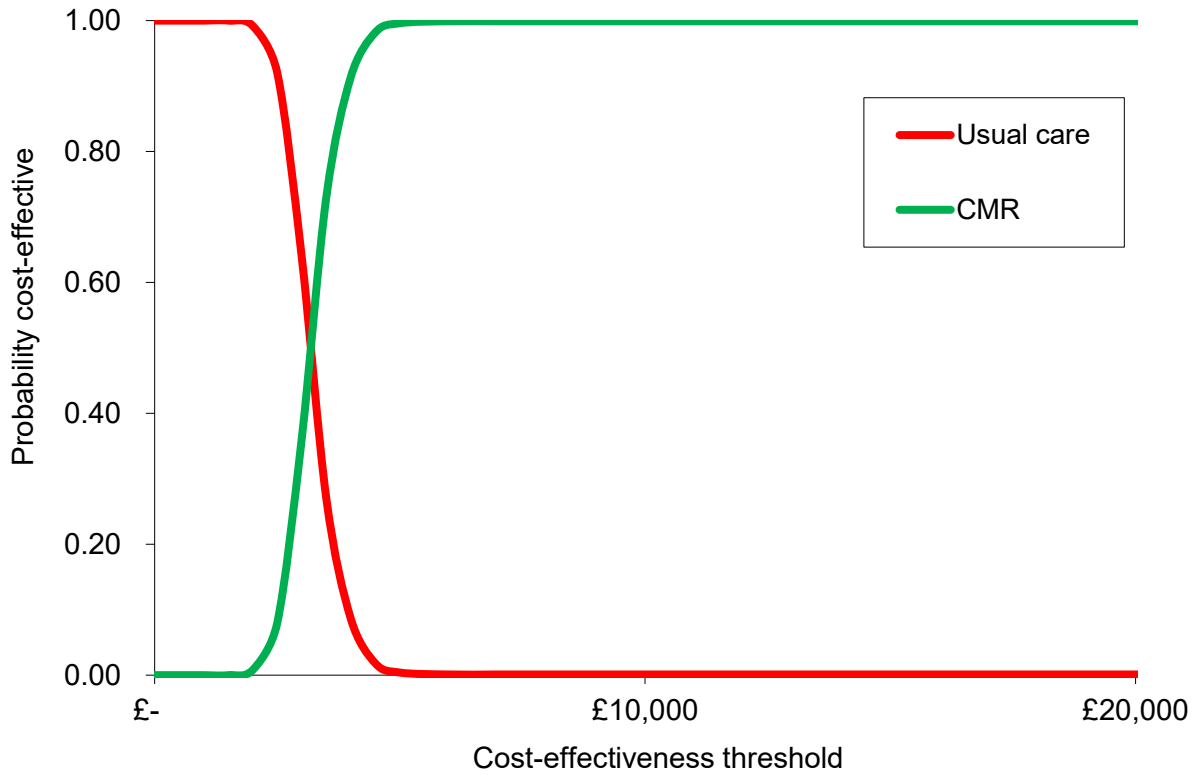
Probabilistic sensitivity analysis (PSA) was carried out for 10,000 simulations, using second-order Monte Carlo simulations, and the values were then plotted on a cost-effectiveness acceptability curve (figure 6.9), which indicates the probability of CMR being cost-effective in relation to the different cost-effectiveness thresholds.

Cost-effectiveness acceptability curve

Probabilistic sensitivity analysis (PSA) shows that with the cost-effectiveness threshold suggested by NICE of £20,000-£30,000 per QALY, CMR was cost-effective with probability of 99%. If the threshold is assumed to be £10,000 per QALY (threshold considered for health technologies with a very good value) CMR is still cost-effective with a probability of 99%.

The threshold determines what the probability of CMR being cost-effective is. With a very low threshold CMR is not cost-effective, but as the threshold increases, the probability of CMR being cost-effective increases. The cut-off point at which CMR begins to become the more cost-effective option is when the threshold is equal to £3,147 per QALY; at this point there is more than 50% chance that CMR is the more cost-effective option.

Figure 6.9 Probabilistic sensitivity analysis: cost-effectiveness acceptability curve



Cost-effectiveness plane

The results of the PSA are also presented as a scatterplot on a cost-effectiveness plane (figure 6.10), which has four quadrants:

a. South-east (SE) quadrant (where CMR dominates UC by being more effective and less costly),

b. North-west (NW) quadrant (where CMR is dominated by UC by being less effective and more costly),

c. North-east (NE) quadrant (where CMR is more effective, but also more costly),

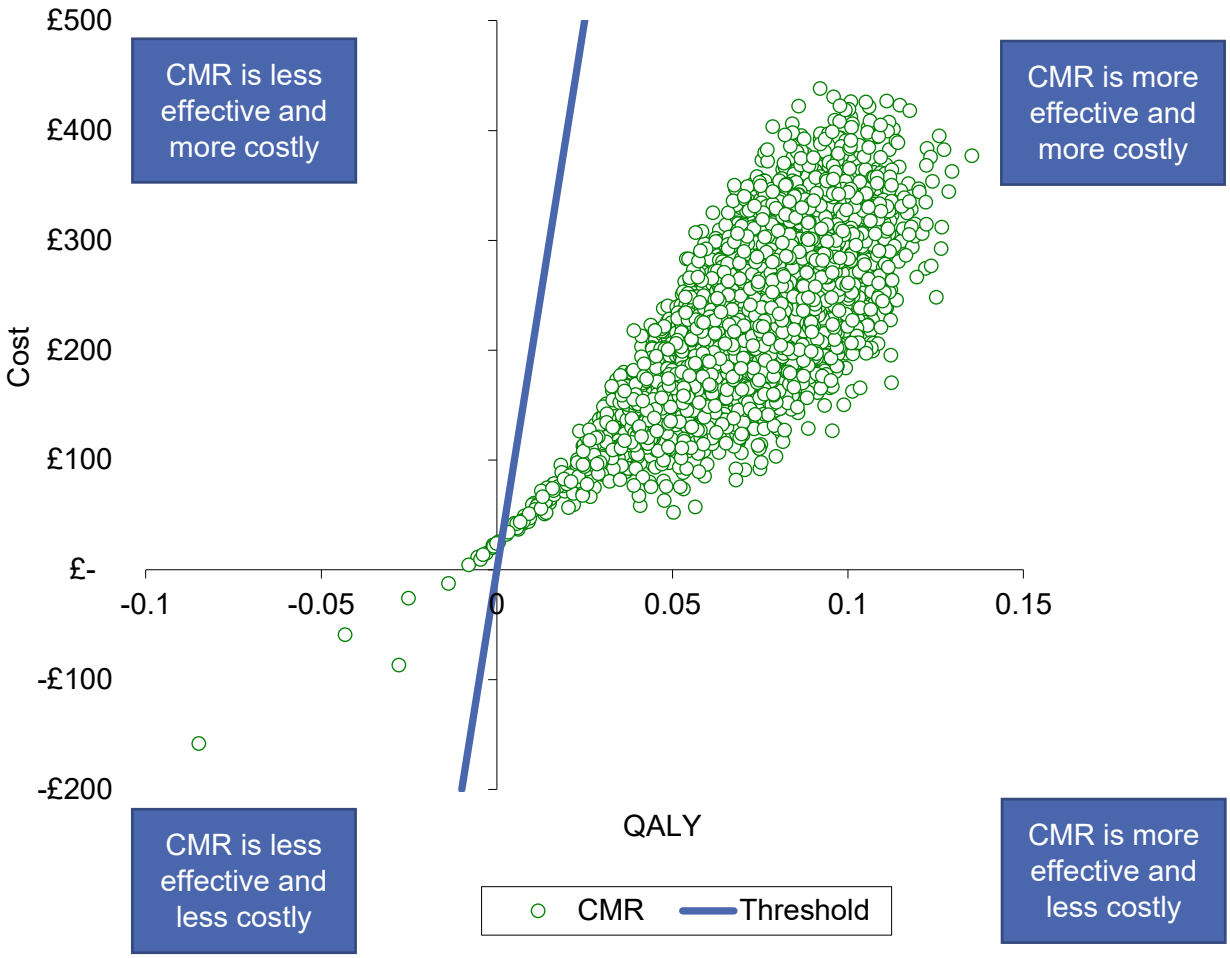
d. South-west (SW) quadrant (where CMR is less effective, but at the same time less costly)

(Klok & Postma, 2004)

99% of results were located in the NE quadrant, which indicates CMR is more effective but also more costly. Of the 10,000 simulations, only 20 results were

outside the NE quadrant, 15 (0.0015%) were in the SW quadrant where the CMR is less effective and less costly, and five results (0.0005%) were in the NW quadrant, where the CMR was dominated by usual care and hence was less effective and more costly. On the cost-effectiveness plane a line is drawn which indicates a cost-effectiveness threshold, which is at ICER of £20,000 per QALY as per NICE guidelines. Every simulated result below that line is deemed cost-effective and would usually be recommended by NICE to be made available for patients.

Figure 6.10 Probabilistic sensitivity analysis: cost-effectiveness plane



With 10,000 simulation iterations, the mean ICER was £3,143.94 per QALY, with CMR on average providing 0.07 QALY gain and increasing the costs by £227.88. The results from PSA are summarised in table 6.23, where the mean values of cost and effects of CMR and usual care are presented.

Table 6.23 Probabilistic sensitivity analysis: average results from 10,000 second-order Monte Carlo simulations

Options	Cost	QALY	ICER
CMR	£4,856.41	2.37	£3,143.94 per QALY
Usual care (UC)	£4,628.53	2.29	
Difference between CMR and UC	£227.88	0.07	

Alternative assumptions and data inputs

None of the sensitivity analyses changed the conclusions of the overall analysis. The assumption where PIP prevalence was altered to represent all patients in the UK (data based on 1,019,491 people in the UK) showed that CMR was still a cost-effective intervention with an ICER of £3,123 per QALY.

Another assumption looked at the change in the discount rate from 3.5% (both for benefits and cost) to 1.5%. The ICER was not very sensitive to this change at £3,089 per QALY and CMR was still cost-effective. Parameters were also changed based on alternative data sources available in the literature and included the alternative assumptions for utilities and costs. For the changes in the utility parameters the ICER ranged from £2,176 per QALY (for changes of utilities for stable HF) to £3,138 per QALY (for exacerbation of HF). The ICER for changes in cost parameters ranged from £3,087 per QALY (for the cost of hospitalisation because of hyponatremia) to £3,144 per QALY (for the hospitalisation cost of exacerbation of HF). All the results from the PSA for alternative data and input parameters are displayed in table 6.24.

Table 6.24 Probabilistic sensitivity analysis: average results from 10,000 simulations

Parameter	Change made in sensitivity analysis	Incremental cost	QALY gain	ICER (£/QALY)	Probability of cost-effectiveness with different cost-effectiveness thresholds		
					£4,000	£10,000	£20,000
Base case analysis		**£245**	**0.08**	**3,123**	**91%**	**99%**	**99%**
Prevalence of PIP	General population rates	£73	0.02	4,469	20%	99%	99%
Discount rate	Changed from 3.5% to 1.5%	£251	0.08	3,089	93%	99%	99%
Utilities	Stable HF	£226	0.10	2,176	99%	99%	99%
	Falls	£227	0.07	3,133	91%	99%	99%
	Hyponatremia	£227	0.07	3,129	91%	99%	99%
	Exacerbation of HF	£227	0.07	3,138	92%	99%	99%
Costs	Falls	£223	0.07	3,091	86%	99%	99%
	Hyponatremia	£222	0.07	3,087	92%	99%	99%
	Exacerbation of HF	£228	0.07	3,144	91%	99%	99%

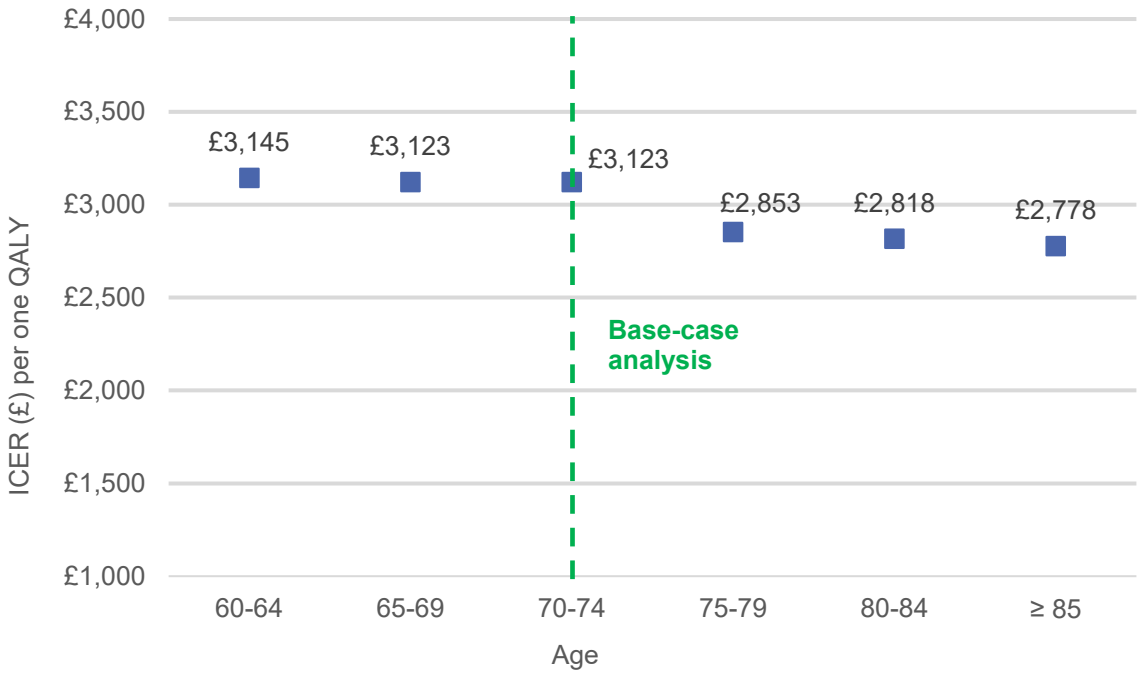
PIP, potentially inappropriate prescribing; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; HF, heart failure

6.4.4 Subgroup analyses

Patients' age

The results of subgroup analyses confirmed the findings from chapter 4, that the higher the age of patients the more cost-effective CMR becomes. The results suggest a small downward trend in terms of ICER as the age of the patient in the model is increased. In the base-case analysis the age at which the patient enters the model was 70. Figure 6.11 presents findings for broader age groups, where ICER per one QALY ranges from £3,145 for 60-64-year-olds to £2,778 for ≥ 85-year olds. All the results in the subgroup analysis are below the £10,000 and £20,000 cost-effectiveness thresholds. The QALY gain is greater the sooner the patient receives CMR intervention, with QALY gain of 0.09 for the 60-64-year-olds and 0.05 for the ≥ 85-year-olds. However, the cost of delivering intervention is higher for younger patients, because life expectancy is longer and hence they can receive CMR for a longer period. The incremental cost per patient in the CMR group is £291 for the 60-64-year-olds and £150 for the ≥ 85-year-olds.

Figure 6.11 Incremental cost-effectiveness ratio in relation to patients' age

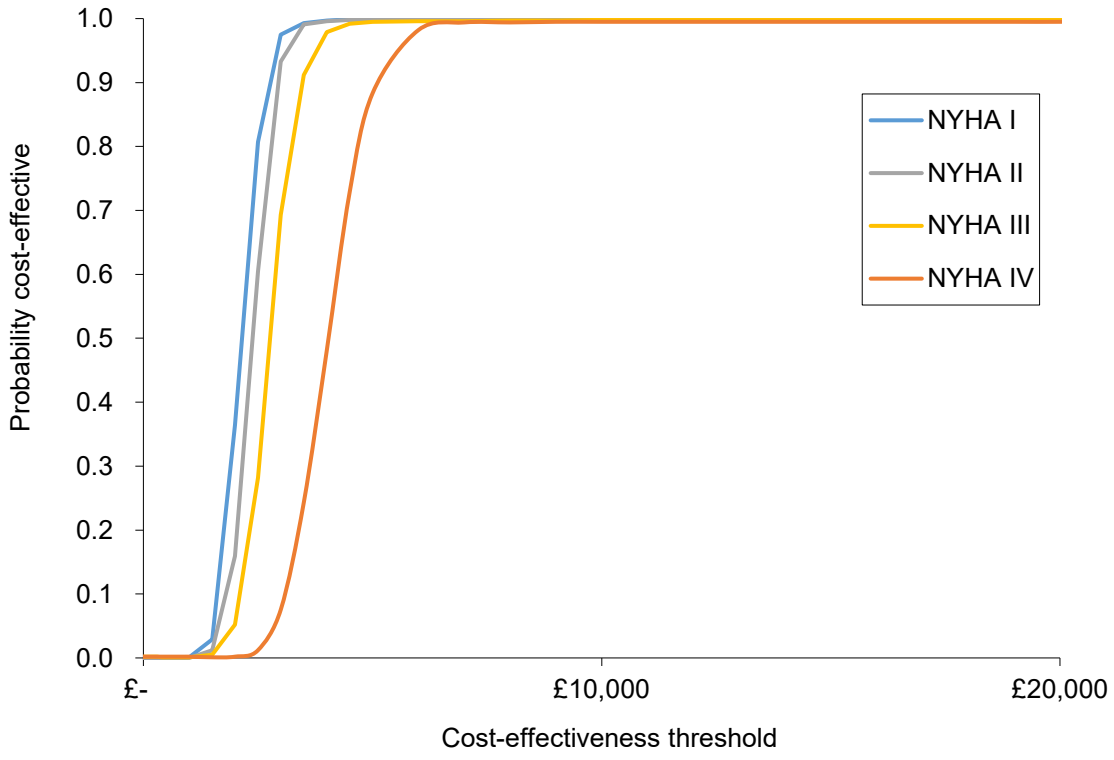


Severity of HF based on NYHA classification

Subgroup analysis was conducted based on the severity of HF, where the utility values for stable HF and hospitalisation because of exacerbation of HF were modified to represent each of the four groups of patients based on the NYHA classification with NYHA class I the mildest and IV most severe.

The PSA with 10,000 simulations was conducted and a cost-effectiveness acceptability curve was fitted for all the NYHA groups (figure 6.12). All four groups had 99% probability of being cost-effective (using the threshold of £20,000 per QALY). The milder the disease, the more cost-effective CMR was, reflecting a bigger QALY gain for patients with less severe HF. Patients with NYHA I have a better prognosis than patients in the NYHA IV group. The QALY gain is higher in NYHA I patients because of increased quality of life and longer life expectancy, during which they can have CMR intervention.

Figure 6.12 Cost-effectiveness acceptability curves for the NYHA classification for severity of HF



6.5 Discussion

The chapter looked at the long-term (lifetime horizon) cost-utility of CMR compared with usual care for hospitalised patients with HF, from the perspective of the UK NHS and PSS. The study found it highly likely that CMR is a cost-effective intervention, where with the cost-effectiveness threshold of £20,000 there was a 99% probability of CMR being cost-effective. The same results hold true when the threshold is reduced to £10,000 per QALY, meaning that CMR can be considered an intervention which offers exceptional value for money.

6.5.1 Contribution to the field

To my knowledge this is the first study that looks at cost-effectiveness of CMR in hospitalised patients with HF. I did not identify studies that looked at this topic in the international literature. Therefore, I will discuss the results of this chapter in the light of two studies (study from chapter 4 of this PhD and (Moriarty *et al*., 2019)) that studied a different research question but had a similar underlining purpose.

1. Chapter 4 - short-term cost-effectiveness of comprehensive medication review

In chapter 4, I presented the results from the short-term cost-effectiveness analysis of CMR for a general population of hospitalised patients. Although the target population, the time horizon and outcomes differed in chapter 4 and chapter 6, it is useful to compare the results. In chapter 4, I compare the results with other studies that look at the health economic impact of CMR on hospitalised patients.

The results from chapter 4 suggest that CMR has the potential to be a cost-effective intervention with the sensitivity analysis done on 10,000 simulations, showing there is a 51.37% chance that CMR is a cost-saving intervention over a short timeframe. In chapter 6 with an extended timeframe and a focussed target population (HF patients) the results also indicate that CMR is a cost-effective intervention based on QALY gain, however conducting CMR over a longer timeframe the costs of delivering this intervention increased and in effect CMR, while cost-effective, was not cost-saving. Despite CMR being more costly, the health benefit was significant as in 99% of the simulations the results were below the NICE threshold of £20,000-£30,000 per one QALY gained, which suggest that CMR is a cost-effective intervention. The results

indicated that CMR can be considered an intervention offering exceptional value for money with 99% probability even below the threshold of £10,000 per QALY.

2. Economic impact of potentially inappropriate prescribing (Moriarty *et al*., 2019)

The premise of the cost-effectiveness of CMR is further supported by the Moriarty *et al*. study having used a different approach and methodology. The Moriarty *et al*. study and the study in this chapter are complementary, as they look at the economic impact of deprescribing similar medicines, but they approach the issue from different angles. The purpose of the Moriarty *et al*. study was to determine the economic impact of three potentially inappropriate prescriptions and estimate the cost-effectiveness of potential interventions that could reduce the number of PIPs for adults aged ≥65 years. Moriarty *et al*. explore the problem from the PIP side, so the question is: "what would be the economic impact of a potential intervention that could reduce all PIPs and substitute them with more appropriate medicines?", whereas this chapter provides an example of such potential intervention (CMR) and explores its value for money. CMR does not reduce all PIPs that patients may have, but to date there is no evidence of an alternative intervention capable of achieving that goal. Studies that look at the effectiveness of CMR in reducing PIPs included in this chapter reflect the reality of clinical practice and the ability of an intervention to reduce PIPs.

Moriarty *et al.* describes the results for all three PIPs separately to indicate the cost of a potential intervention to address each PIP separately. The study in this chapter evaluates CMR, which can address the inappropriate prescribing of all three PIPs from the Moriarty *et al.* study and other PIPs.

The results from this chapter are consistent with the results from Moriarty *et al.,* where they conclude that for interventions to reduce PIP, at a threshold of €20,000 per QALY (£17,740[6]) targeting NSAIDs would be cost-effective for interventions up to €1,099 (£974.81[6]) per person, for benzodiazepine €1,101 (£976.59[6]) and for PPI €671 (£595.18[6]). Even with a threshold of £0 the potential intervention would be

[6] The cost was converted using the Bank of England exchange rate from January 2018; 1 EUR = 0.8870 GBP.

cost-effective if it does not exceed the cost of €401 (£355.69[6]) per person for targeting NSAIDs €798 (£707.83[6]) for benzodiazepine and €544 (£482.53[6]) for PPIs. In this chapter, I estimated the cost of CMR at £25.20, which is calculated based on the additional time needed for pharmacists to complete the review (33.6 min) (95%CI 31.9 to 35.5), (Brodersen Lind *et al*., 2016) and an hourly cost of pharmacist work in the UK NHS of £45 (Curtis & Burns, 2018). The additional cost from base-case analysis associated with delivery of CMR was estimated at £244.51 per person, which is well within the cost threshold reported by Moriarty *et al.* Therefore, the results are complementary to the results from this chapter, where there was a 99% probability of CMR being a cost-effective intervention with the cost-effectiveness threshold of £20,000 per QALY.

The similarity between the study in this chapter and the Moriarty study is that both studies modelled the economic impact of similar PIPs. Moriarty *et al*. used three PIPs in the analysis: proton pump inhibitors, NSAIDs and benzodiazepines; these are the same PIPs that I use in my analysis. In my model, apart from these three PIPs I also look at neuroleptic drugs, duplication of drug classes and thiazide diuretics.

With the few differences already mentioned, the two studies also differ in the study population and health setting. The target population studied in this chapter are hospitalised 70-year-old patients with HF vs a general population of 65-year olds in the Moriarty *et al.* study. This study is a UK NHS and PSS perspective where Moriarty *et al.* used the Irish health system.

Health economics of complex intervention

Chapter 2 demonstrated a gap in the literature regarding the agreed approach to health economic evaluation of complex interventions. Methods of economic evaluation have primarily been applied to pharmaceuticals as the formal requirement for assessment of cost-effectiveness of new medicines on the market (Drummond *et al*., 2015). However, using traditional economic evaluations in order to assess the economic impact of complex intervention has associated challenges (more detail in section 1.3.2.4 ‘Economic evaluation of complex interventions’).

A few frameworks look at evaluation of complex healthcare interventions such as the MRC Framework on Developing and Evaluating Complex Interventions (Craig, Dieppe, Macintyre, Mitchie, *et al*., 2008), the Institute of Health Economics discussion paper on economic evaluation of complex health system interventions (Husereau *et al*., 2014), the methods for the development of NICE public health guidance (NICE, 2012) and NICE evidence standards framework for digital health technologies (NICE, 2019). The guidelines focus on drawbacks of the traditional extra-welfarism approach in conducting cost-effectiveness analysis of complex interventions. The solutions proposed by these frameworks allow minor adjustments in existing evaluations. They explore different solutions and new approaches that could facilitate the economic evaluation.

This study showed that it was possible to use the traditional extra-welfarism theoretical framework to evaluate the cost-effectiveness of complex interventions such as CMR. With detailed modelling approaches it was possible to evaluate some of the complex interventions by using traditional methods. The study from this chapter gave special consideration to the six aspects of complexity described by IHE (Husereau *et al*., 2014) that require special attention when doing economic evaluation of complex interventions.

6.5.2 Contribution to thesis and implications for further research

6.5.2.1 Contribution to thesis

This study directly addresses the main gap in the literature identified in chapter 1 and addresses the aim of the PhD as a whole, which is the investigation of cost-effectiveness of CMR in the context of UK NHS hospitals.

This chapter builds upon all the previous chapters, which provide valuable input which gives a sound basis for this chapter. Chapter 1 described the research question that needs to be addressed. Chapter 2 presents the possible challenges in economic evaluation of complex interventions such as CMR, and the way these challenges can be addressed. Chapter 3 provides some data about the cost of medicines with both CMR and usual care used as parameters in the model in this chapter, while chapter 4 provides early evaluation of the cost-effectiveness of CMR

for the general population and makes suggestions for the issues to be addressed in the long-term cost-effectiveness model. Chapter 5 narrows down the target population to patients with HF. All the chapters have contributed to the inputs and hence outputs from this chapter. The results demonstrated that it is highly likely that CMR is a cost-effective intervention for hospitalised patients with HF over an extended timeframe.

6.5.2.2 Further research

Further research can be summarised in three potential study areas:

1. Conducting health economic evaluations of complex interventions

The study presented in this chapter is an example of the use of traditional health economic approaches with six key recommended adjustments (described in chapter 2) to conduct cost-effectiveness analysis of complex interventions. The analysis was possible with complex modelling and by being mindful of the underlying assumptions. Further research is required to understand in what situations it is possible to use traditional methods and when other methods to evaluate economic impact of complexity are necessary. The study from this chapter may serve as a case study describing a successful attempt at evaluation of complex intervention using traditional extra-welfarism methods.

2. Economic evaluation of interventions optimising prescribing

Most economic evaluations concentrate on new health technologies, for example a new medicine released on the market, a new surgery procedure or a new public health intervention (such as a smoking cessation program). These new interventions often add cost to the already strained health budgets, and some may add more pressure to the daily obligations of already busy healthcare professionals. The tendency to include new technologies overshadows interventions that already exist and can be improved. Medicines optimisation and improving prescribing quality are good examples of how existing technologies such as medicines already available on the market can be improved. Study from this chapter provided indication that interventions aimed at improving existing care (CMR), rather than creating new patterns of care, can be highly cost-effective. Further research can focus on

cost-effectiveness analysis of existing interventions aimed at improving prescribing quality or improving general quality of care.

3. Further cost-effectiveness analysis of CMR

The study in chapter 4 provided information on the short-term cost-effectiveness of CMR applied to a general population from UK NHS acute care. This chapter expanded this to a long-term cost-utility analysis for patients with HF in NHS hospitals. However, CMR is a complex intervention that can be applied in various settings, by different healthcare professionals, for different patients and using different tools. Research can focus on evaluation of the economic impact of different forms of CMR. The focus could be directed at other patients that may require CMR. For example, a modelling approach similar to that developed in this chapter could be used to evaluate cost-effectiveness of CMR for COPD patients. Like HF patients, patients with COPD have significant comorbidities and high mortality and experience high incidence of potentially inappropriate prescribing and problematic polypharmacy. COPD is also associated with frequent hospital admissions and readmissions and hence is a significant economic burden. For all these reasons, COPD would be a good candidate condition for conducting economic analysis of CMR.

6.5.3 Strengths and limitations

The study presented as part of this chapter is the first cost-utility analysis of CMR vs usual care for hospitalised HF patients in the NHS. The biggest strength of the study is that it provides evidence of cost-effectiveness of an intervention that can play an important part in daily care for hospitalised patients in the UK.

A strength of the study is that it uses best practice that already exists in health economics and is based on the extra-welfarism theoretical framework. The study follows NICE guidance for the methods of technology appraisal and uses methods recommended in the ‘reference case’ (NICE, 2013b). CMR is a complex intervention that could potentially prevent researchers from using traditional methodology, because they might assume it is too complex for a traditional economic model. However, this study uses a sophisticated model with deliberate assumptions that

allow the cost-utility analysis to be completed and provide the results as incremental cost-effectiveness ratios.

The model is a combination of decision tree and Markov models, which allow us to look at the immediate effect of CMR on prescribing in combination with long-term modelling of the impact of inappropriate prescribing on patients' health and the costs associated with treatment. Extensive sensitivity analyses were conducted to test the level of confidence in the conclusions of the economic evaluation. The results of the sensitivity analyses confirm the firmness of the conclusions, where in most cases the results were not sensitive to changes in model assumptions, which provides strong indication that CMR is cost-effective.

The study has some limitations that need to be acknowledged. It requires several assumptions about the healthcare system organisations and the mechanisms of effects that could influence the delivery of the intervention. Even with a robust approach to analysing uncertainty, these assumptions cannot easily be tested in the sensitivity analyses. However, the PhD focuses mainly on addressing the complex nature of the intervention, rather than that of the wider healthcare system in which it is delivered.

Another limitation of the study is that only the six most common PIPs as measured by STOPP/START criteria for patients with HF were considered in the analysis. Although this is a limitation, it can be considered a conservative assumption, as there could potentially be more PIPs that could be deprescribed by the delivery of a CMR intervention. STOPP/START criteria are also not the only potentially inappropriate prescriptions that could be prescribed to HF patients. A Consensus Potentially Inappropriate Medicines in Heart Failure (PIMHF) list was developed by (Bermingham *et al*., 2014) to measure other potentially inappropriate medicines that are specific for patients with HF. Therefore, there could potentially be additional health benefits for patients who receive CMR compared to usual care.

Only the major and well evidenced adverse events of each PIP were included in the economic model. There could potentially be more adverse drug events and drug on drug interactions not accounted for in the model. This is also a conservative

assumption, because the CMR could potentially reduce more adverse events than the ones included in the model.

A further limitation was the fact that it was not possible to account directly for different comorbidities in the model. It was looked at indirectly, because the study does not limit patients by the number of medical conditions that they may have concurrently, as long as one of these conditions is HF. In fact, the medicines included in the cost-effectiveness analysis suggest that the patients have multiple comorbidities. Neuroleptic medications are used for treatment of psychiatric disorders, and benzodiazepines for treatment of anxiety, so some of the patients may suffer from mental health conditions. Proton pump inhibitors are medicines used to treat ulcers, thiazide diuretics are prescribed for hypertension and NSAIDs are pain relievers. This suggests that additional medical conditions are present in the study population, hence comorbidity is indirectly looked at in the model.

The assumption in the model was that the exposure to PIPs was sustained until patients received a CMR intervention, where the PIP could be deprescribed. In fact, patients may more often switch from being on PIPs to not being on PIPs and vice versa. The model did not look at the effect of treatment adherence.

There is a wide range of drugs that could be prescribed in place of PIPs, dependent on the individual treatment regime of the patient; therefore it was not possible to look at treatment effects and adverse effects of alternative medicines prescribed in place of PIPs. However, again this can be considered a conservative assumption, as there is a strong evidence base from STOPP/START literature that suggests medicines prescribed in place of PIPs are usually safer, more effective or less costly. In the model, only the cost of alternative medicines was considered, which was based on data from the ReMAC study (see more detail in section 6.1.3.3 ‘Cost and resources’). The full cost data were available for 83 patients and related to the cost of medicines prescribed in place of PIPs (PPI, benzodiazepines, any duplicate drug class prescription, thiazide diuretics, NSAIDs or neuroleptic drugs).

The model is based on evidence that can be considered heterogenous: for example, the effectiveness of CMR in reducing PIPs in each study from the systematic literature review (Hill-Taylor *et al*., 2016) was different, but in all the studies it was

effective; just the size of the effect varied. This can be explained by the fact that effectiveness of CMR may differ depending on the setting, who performs the CMR and the quality of the CMR delivered. The sensitivity analysis showed that even if CMR only reduced the PIP burden by 10% it would still be cost-effective.

Another example of heterogeneity was that STOPP/START criteria are based on drug classes with a broad range of medicines, so their cost, effectiveness and safety may vary. Different NSAIDs may have different impacts on the number of adverse effects (exacerbation of HF), but all the NSAIDs included in the model increase the risk of exacerbation of HF but with different ratios. The hazard ratios were pulled together in a meta-analysis and 95% CI were used in the PSA. The patient groups may also vary, with some high-cost groups of patients and some that gain more QALYs. Therefore, the population was narrowed down to patients with HF, and further subgroup analysis was conducted for different age groups and for type of HF based on severity measured by NYHA classes.

Finally, PIPs, as the name suggests, are potentially inappropriate medicines, therefore there can be cases in which these medicines will provide more benefit than harm and are still prescribed. The model is based on real-life evidence from RCTs in which pharmacists, doctors and patients decided together with the help of a CMR intervention whether a PIP should or should not be deprescribed. Therefore, the model already incorporates clinical decision and recognises that some PIPs may still be needed for the patient. There are cases in which CMR results in deprescribing PIPs which after discharge are prescribed again by another physician. However, one of the RCTs (Frankenthal *et al*., 2014) on which the model is based conducted a follow-up trial after 24 months to see whether the effects of the CMR intervention were sustained (Frankenthal *et al*., 2017). The authors conclude that the effect of CMR using STOPP/START criteria was maintained over time.

6.6 Conclusions

In conclusion, the study provided evidence that CMR conducted according to STOPP/START criteria for patients with HF is a cost-effective intervention over a lifetime horizon in the NHS. The results are mainly driven by the relatively low additional cost associated with the CMR intervention. The second-order Monte Carlo

simulation carried out for 10,000 simulations indicated that the additional cost associated with the CMR on average equalled £227.88, whereas the QALY gain was 0.07. This resulted in an ICER of £3,143.94 per QALY, which is well below the cost-effectiveness threshold of £10,000 per QALY and below the threshold of £20,000-£30,000 per QALY recommended by NICE. In 99% of the simulated results the ICER was below this threshold, providing evidence that CMR should be considered a cost-effective option for patients with HF in NHS hospitals.

Results of the subgroup analysis are consistent with the results from chapter 4 and further suggest that the cost-effectiveness of CMR increases with age. Additional analysis that looked at severity of HF based on NYHA classification showed that the milder the HF, the more cost-effective CMR becomes.

The deterministic analysis indicated that there are four parameters (effectiveness of CMR in reducing PIPs, type of PIPs, cost of substitute medicine prescribed instead of PIP and prevalence of PIP) in the model with most uncertainty around their value. Additional analysis for the four parameters showed the results were not sensitive to change of these parameters and hence conclusions remained the same. The results of the analysis showed that even if CMR was only 10% effective in reducing the number of PIPs, it still would be cost-effective and that if only 1% of the population had PIPs prescribed, CMR would still be a cost-effective intervention. This study suggests that CMR applied well should be a routine part of hospital care, probably targeted at older patients with co-morbidity and/or specific target conditions.

CHAPTER 7 DISCUSSION AND CONCLUSIONS

This chapter gives the overall overview of the thesis and presents the answers to each research question set up in the introduction. It also presents the main findings from the PhD thesis and highlights the empirical and methodological contributions for the literature and field of health economics. The chapter also highlights some areas for further research and presents implications of the PhD on policy and practice. The impact of the study design is discussed, and key limitations acknowledged. The chapter ends with the conclusion and key messages of the PhD.

7.1 Thesis overview

Chapter 1 is an introduction chapter that highlights background literature about problematic polypharmacy and the solution to tackle it through medicines optimisation activities. A wider view of the global economic impact of medicines is presented along with detail about the spending on medicines in the UK. The chapter provides information about CMR, which is a key aspect of medicines optimisation. Gaps in the literature are identified in connection to economic analysis of CMR, the understanding of ways in which CMR is applied in hospitals, the complexity of CMR and the appropriate target population that should receive CMR. Based on the identified gaps, the aim was clarified: to investigate the cost-effectiveness of CMR in the context of UK NHS hospitals. Subsequently, five research questions are developed to help achieve the aim. Each of the chapters of the PhD is aimed at answering one of the five research questions set out in the introduction.

Research question 1

In what way does CMR qualify as a complex healthcare intervention? How does complexity of CMR influence the evaluation of its cost-effectiveness?

Chapter 2 addresses research question number 1 by presenting results of a scoping literature review about complexity of CMR and its influence on the cost-effectiveness analysis of this intervention. Fifteen studies were included in the scoping review: three cost-effectiveness studies (Gallagher *et al*., 2016; Ghatnekar *et al*., 2013; Wallerstedt *et al*., 2012), six studies describing the CMR intervention (Bulow *et al*.,

2018; Graabaek *et al*., 2015; Jubraj *et al*., 2015; Lennox *et al*., 2019; Szymanski *et al*., 2016; Ward *et al*., 2019), one national guidance (NICE, 2015a), and five systematic literature reviews (one of which was an update published after the NICE guideline was published) (Christensen & Lundh, 2013, 2016; Graabaek & Kjeldsen, 2013; Hill-Taylor *et al*., 2016; Hohl *et al*., 2015).

Literature was analysed using thematic analysis based on the Institute of Health Economics (IHE) framework that described six key criteria that need to be considered when conducting economic evaluation of complex interventions (Husereau *et al*., 2014). For each of the six criteria, the standard economic evaluation approach is presented, then the challenges in relation to the six criteria when a complex intervention is evaluated are shown.

The key considerations for economic evaluations of CMR regarding six IHE criteria were:

- Valuing outcomes: Studies have shown effectiveness of CMR in terms of intermediate outcomes such as reduction in emergency department admissions or potentially inappropriate prescribing. These outcomes can serve as a vehicle to evaluate the economic impact of CMR.
- Comparators: CMR is already in place in the UK, however its consistency and quality could be improved (Szymanski *et al*., 2016; Ward *et al*., 2019). The comparator used for the analysis can be usual care defined as medication review done inconstantly, low quality medication review, ad hoc medication review or noncomprehensive medication review.
- Perspective: It might be important to look at cost-effectiveness of CMR from a broader perspective that includes benefits and costs for different stakeholders.
- Effectiveness: Context is a critical determining factor in the success of CMR. Therefore, the behavioural factors and systemic factors may be considered in the analysis.
- Resource use and costs: The main resource used for delivery of CMR – the time of a healthcare professional – is case sensitive. It is important to account for variation in delivery of CMR across different settings and in different contexts.

- Modelling: Results from studies might not reflect long-term outcomes. We assume that the QALYs can be estimated based on intermediate outcomes.

Complex system interventions like CMR are difficult to evaluate given the scope and number of factors to consider. It is essential to account for context and complexity when conducting a cost-effectiveness analysis of CMR.

Research question 2

How is CMR applied in inpatient hospital settings and what is the impact on prescribing patterns and costs?

Chapter 3 answers research question number 2 by presenting the effect of CMR on the overall polypharmacy burden and the impact of CMR on the number of medicines deprescribed, started and held. This chapter also compares the cost of the deprescribed medicines between CMR and usual care groups. The analysis used Review of Medicines in Acute Care (ReMAC) initiative data and British National Formulary (BNF) data to understand the difference in prescribing patterns and costs. ReMAC was a prospective, multicentre (five acute hospitals in North West London), nonrandomised, quality improvement initiative carried out between April 2015 and July 2016 (Szymanski *et al*., 2016; Ward *et al*., 2019). The aim of ReMAC was to improve medicines optimisation for older patients aged ≥ 70, by optimising the delivery of medication review. To evaluate the effectiveness of the ReMAC initiative researchers retrospectively analysed discharge summaries (DSUM) and patients' notes to find documented evidence of medication review.

I analysed the data from the ReMAC study and compared patients who received CMR with patients who received usual care. Data were collected for 3,043 patients and four analyses were conducted: (1) analyses of patient characteristics using descriptive statistics; (2) comparison of the mean number of medicines deprescribed, held, and started between CMR and usual care group using t-test; (3) comparison of the mean cost per patient of the deprescribed medicines between the CMR and usual care groups, using the t-test; (4) a three-way ANOVA (2x2x5) intended to test the effect of CMR on the difference between medicines on discharge and medicines on admission and subsequent analyses to test whether a three-way interaction effect

exists between CMR, age and gender in explaining the difference in number of medicines.

For the costing of medicines, cost values were attached to each of the 10,856 deprescribed or started medicines through a manual search of the British National Formulary (BNF) website for data on cost and standard daily dose of medicines.

Analysis 1: Patient characteristics

The median age of patients was 83 years (Q1: 77; Q3: 88). 52.9% of patients were female. The mean number of medicines on admission for both groups was 7.79 on admission and 8.84 on discharge. There were 1,062 patients with a documented CMR and 1,981 patients who received usual care.

Analysis 2: Patterns of prescribing

Receiving a CMR affects the number of medicines:

- Deprescribed
  On average, patients in the CMR group had more medicines deprescribed per person ($\bar{x}$ = 1.44, SE = 0.06) than the usual care patients ($\bar{x}$ = 0.97, SE = 0.04) and the difference was statistically significant ($p \leq 0.0125$).
- Held
  Patients receiving CMR had more medicines held per person ($\bar{x}$ = 0.21, SE = 0.02) than the usual care patients ($\bar{x}$ = 0.14, SE = 0.01), with the difference being statistically significant ($p \leq 0.0125$).
- Started
  The CMR also resulted in more new medicines being started per person ($\bar{x}$ = 2.68, SE = 0.07) than the usual care group ($\bar{x}$ = 2.36, SE = 0.05), with the difference being statistically significant ($p \leq 0.0125$).

Analysis 3: Cost of the deprescribed medicines

The saving from deprescribing medicines was -£2.78 per month per patient larger in the CMR group ($\bar{x}$ = -£9.67, SE = 0.46) than in the usual care group ($\bar{x}$ = -£6.89, SE = 0.27).

Analysis 4: The effect of CMR, gender and age on number of medicines

- There was a statistically significant main effect of CMR on the difference between the number of medicines on discharge and on admission ($F(1, 2,306) = 40.51$, $p < 0.05$). This suggests that CMR compared with usual care was associated with reduced polypharmacy burden after the intervention.
- There was a not significant main effect of age ($F(4, 2,306) = 1.93$, $p = 0.103$) or gender ($F(1, 2,306) = 0.03$, $p = 0.853$) on the difference in the number of medicines.
- There was a borderline statistically significant interaction effect between all three variables: CMR, age and gender ($F(4, 2,306) = 2.33$, $p = 0.054$). This suggests that even though CMR was the main contributing factor to the difference in the number of medicines, the effectiveness of CMR was affected differently for different genders and age groups. Two-way analysis found an interaction effect between CMR and age, as well as between age and gender of patients.

Research question 3

Is CMR a cost-effective intervention for the general population of elderly acutely hospitalised patients, over a short-term (12-month) time horizon, compared with usual care, from the perspective of the UK NHS?

Chapter 4 addresses research question number 3 by presenting findings of a de novo created short-term cost-effectiveness model of CMR vs usual care for the general population of older patients acutely admitted to a UK NHS hospital. The study provides evidence that a pharmacist-led CMR has the potential to be a cost-saving intervention within a 12-month time horizon. The model was constructed as a decision tree model in which patients receiving CMR or usual care had different probabilities of experiencing ED reattendance within 12 months. The cost of CMR was assumed to be the additional time needed for a pharmacist to complete the CMR intervention and it was estimated at a unit price of £25.20 (SE = 0.03). In the base-case analysis the probability of having an ED admission was 0.16 lower in the CMR group compared to the usual care group and the CMR also provided savings of £0.28 per patient. This indicated that in the base-case analysis CMR dominated over

usual care by being more effective and less costly. The conclusions were tested through Probabilistic Sensitivity Analysis for 10,000 second-order Monte Carlo simulations. The results indicated that there was 51.37% probability that CMR was a cost-saving intervention. The probability of CMR being cost-effective increased to 80% if the decision makers would be willing to pay £117 per one ED reattendance adverted. Further analysis indicated that CMR which takes no longer than 33 minutes for a pharmacist to complete was cost-saving.

Results were also tested for a subgroup of patients based on age and for different healthcare professionals delivering the intervention. CMR cost-effectiveness increased with age of patients, where ICER values equalled £1.78; -£1.77; -£5.50; -£8.36; -£10.61, for the age groups of ≥60; ≥65; ≥70; ≥75; ≥80 respectively. In the deterministic sensitivity analysis, the assumption was changed to see how cost-effectiveness of CMR changes depending on which healthcare professional is delivering it. In the base-case analysis, CMR was delivered by a pharmacist. For the following professions: pharmacist specialist, pharmacist – advanced, pharmacist – team manager, pharmacist consultant, associate specialist, and consultant: medical, ICER was higher than in the base-case analysis (meaning it was less cost-effective than in the base-case, but still might be cost-effective). The CMR was more cost-effective than in the base-case analysis when the intervention was delivered by a registrar, hospital-based nurse, or foundation doctor FY2 or FY1. However, the quality of medication review delivered by different healthcare professionals may differ.

The chapter provided a way forward in the PhD by indicating that pursuing the analysis of long-term cost-effectiveness is worthwhile. However, in order to do that, narrowing down the target population was required. The long-term cost-effectiveness model should also include estimating the potential gain in QALYs from CMR.

Research question 4

What are the target populations of patients acutely admitted to hospital who could benefit from CMR? Out of those, which population should be included in the modelling of long-term cost-effectiveness of CMR?

Chapter 5 follows the recommendations made in chapter 4 and determines what the target populations of patients acutely admitted to hospital who could benefit from CMR are. By doing so, the chapter answers research question number 4 and provides information for chapter number 6 on target population that should be included in the modelling of long-term cost-effectiveness of CMR.

I conducted a literature review that looked at guidelines on medicines optimisation and polypharmacy. The literature review resulted in identifying four key domains that would help to narrow down the target population. The four domains that reflect the characteristics of the target population for CMR were: (1) public health importance of the medical condition (key measures: admission rate, in-hospital mortality rate); (2) polypharmacy (key measures: in-hospital mortality rate, emergency admission rate; emergency readmission rate within one month, economic burden, potentially inappropriate prescribing rate); (3) chronic care conditions (acute conditions were excluded from the analysis); (4) age (population of elderly was selected). Based on the four domains, a decision model was created to select one target population.

The data for the model came from routinely collected Summary Hospital-level Mortality Indicator (SHMI) data, which helped narrow down the analysis to 10 conditions with the most public health importance. Following that, a targeted literature review was conducted for the following 10 medical conditions: pneumonia, septicaemia, acute cerebrovascular disease, congestive heart failure (HF); COPD, urinary tract infections, acute myocardial infarction, fracture of hip, acute bronchitis and gastrointestinal haemorrhage. The literature review identified 893 unique publications, out of which 59 articles met the inclusion criteria.

Out of the 10 analysed conditions, two conditions, HF and COPD, could be defined as chronic care conditions and were included in further analysis. The conditions bore public health importance, were associated with problematic polypharmacy and were mostly prevalent in older patients. Both conditions were suitable for inclusion in the long-term cost-effectiveness analysis of CMR, but in the end the analysis was conducted for patients with HF. The choice of HF was justified by HF having higher emergency readmission rates, in-hospital mortality and higher economic burden. Therefore, three out of five criteria for problematic polypharmacy favoured the choice of HF as the target population. The chapter provides recommendations for future

research on the cost-effectiveness of CMR for patients with COPD, which was out of scope of this PhD.

Research question 5

Is CMR a cost-effective intervention over a long-term (lifetime) time horizon, compared with usual care for the identified target population, from the perspective of the UK NHS and personal social services (PSS)?

Chapter 6 brings together evidence from all the other chapters in order to address the gap in the literature by answering the final research question. The study directly addresses the main gap in the literature identified in chapter 1 and addresses the aim of the PhD as a whole. The study looked at patients ≥70 years old, with HF, that are hospitalised in the UK NHS. The compared interventions were CMR and usual care and the outcome was presented as Incremental Cost Effectiveness Ratio (ICER), where the benefit was measured in QALY gain and the costs in pounds sterling.

A de novo cost-utility model was developed based on two complementary parts – a short-term decision tree model and a long-term Markov model. The decision tree model looked at the immediate effect of CMR on prescribing by looking at reduction in the rate of potentially inappropriate prescribing (PIPs). The six PIPs included in the analysis were: proton pump inhibitors, benzodiazepines, duplicate drug class prescription, thiazide diuretics, NSAIDs and neuroleptic drugs. The Markov model investigates the effects of changes in prescribing on health benefit measured by QALYs and changes to costs. The model is a six-state Markov chain (two states for stable HF: (1) patient on PIP; (2) patient not on PIP and three states for hospitalisation because of adverse effects of PIPs: (3) hyponatremia; (4) exacerbation of HF; (5) fall and (6) death) with a cycle length of one month and lifetime horizon. The data used to populate the model came from routinely collected Hospital Episode Statistics data, literature reviews, data from the ReMAC study and an evidence base from STOPP/START criteria.

Based on 10,000 second-order Monte Carlo simulations QALY per patient in the CMR group was 2.37 compared to QALY in the usual care group of 2.29, which reflected a QALY gain in the CMR group of 0.07 (the numbers are rounded to the

second decimal place). The cost in the CMR group was £4,856.41 per patient compared to £4,628.53 per patient for the usual care group, which was an increase of cost in the CMR group of £227.88. The ICER per additional QALY gained for CMR versus usual care was estimated to be £3,143.94 per QALY. Probabilistic sensitivity analysis was carried out on 10,000 simulations and showed that there was 99% probability that CMR was cost-effective at a threshold of £20,000- £30,000 per QALY. The results are the same when the threshold is reduced to £10,000 per QALY, meaning that CMR can be considered an intervention offering exceptional value for money. Further PSA analysis was conducted when different sources of data were used for some of the parameters and where assumptions were modified (e.g. prevalence of PIPs for general population of patients instead of only HF patients). The results were not sensitive to this change and the conclusions did not change.

In deterministic sensitivity analysis the best- and worst-case scenario analysis was conducted to test the results if one of the parameters in the model was altered to represent extreme values. Further analysis was conducted on four key parameters:

1. Effectiveness of CMR in reducing PIPs – even if the effectiveness of CMR was reduced to 10% it was still a cost-effective option.
2. Type of PIPs – none of the results changed the conclusion that CMR is cost-effective, except in one case: assumption that the only PIP that the patient may receive is ‘any duplicate drug class’; then CMR was no longer cost-effective.
3. The cost of substitute medicine prescribed instead of PIP – CMR was a cost-effective intervention if the cost of alternative medicines prescribed instead of PIPs did not exceed £134.
4. Prevalence of PIP – the results of the analysis suggest that even with prevalence of PIPs as low as 1%, CMR would still be cost-effective.

Finally, a subgroup analysis was conducted based on age and severity of disease. The results are complementary with the results from chapter 4, which state that CMR cost-effectiveness increases as the age of patients increases. The analysis for severity of HF based on NYHA classification showed that CMR was most cost-effective for patients with HF classified as NYHA I.

7.2 Contributions

7.2.1 Empirical contributions

Cost-effectiveness of CMR

Arguably the biggest empirical contribution that this study adds to the current literature is estimating the cost-effectiveness of hospital CMR compared with usual care from the perspective of the UK NHS and PSS.

NICE guidelines on Medicines Optimisation (NICE, 2015a) provide recommendations for priorities in future research. One of the key priorities was to focus future research efforts on determining whether CMR is more clinically effective and cost-effective compared with usual care at reducing suboptimal medicines use in the UK setting. There were two models that I created which estimate the cost-effectiveness of CMR: one for the general population of acutely hospitalised older patients, where there was a 51% chance that the intervention was cost-saving over a 12-month time horizon (chapter 4) and an 80% chance that it was cost-effective if the decision makers would be willing to pay £117 per one ED reattendance adverted; and a second model which estimated that there was 99% probability that CMR was cost-effective for hospitalised older people with HF over a lifetime horizon. To the best of my knowledge, two de novo models that were created as part of the PhD are the first attempt to look at the cost-effectiveness of CMR in the UK NHS hospital setting.

NICE recommends researching ‘the frequency of medication review’, which can impact on cost-effectiveness of resource use. Chapter 3 presented the results of the ReMAC study which aimed to increase the frequency and quality of delivery of CMR in five acute trusts in NWL. At baseline, CMR was recorded on average in only 4% of patients from the eligible population, but by the end of the study the average had increased to 63% of the eligible population (Szymanski *et al*., 2016; Ward *et al*., 2019).

The NICE guidelines on Medicines Optimisation (NICE, 2015a) also recommend a format of research for the evaluation of CMR. The PhD addresses some of the key recommendations proposed by NICE. The recommendations were made for evaluating the clinical effectiveness of CMR, but they are also valid for health economic research. The contribution of the PhD based on NICE recommendations is presented in table 7.1.

Impact of CMR on reducing overall polypharmacy burden, prescribing patterns and costs

The study informs the literature by providing new information on how receiving CMR impacts the change in the number of medicines. Compared to usual care, CMR was associated with significantly more changes to the medication, both newly prescribed and deprescribed or held. CMR was also associated with a decreased overall polypharmacy burden: the difference between the number of medicines on discharge and on admission was lower in the CMR group than in the usual care group. The new evidence coming from the PhD fills the gap in the literature about how CMR reduces overall polypharmacy burden and what the mechanisms driving this change are. The reduction in polypharmacy was mostly driven by deprescribing of medicines. This was also associated with cost savings per patient from deprescribed medicines of -£2.78 per patient per month.

The analysis also shows that from the three variables CMR, gender and age, only CMR had a significant main effect on the difference in number of medicines, with patients who received CMR having fewer additional medications at discharge than usual care patients.

Table 7.1 PhD contribution towards NICE recommendations for proposed format of research on evaluating CMR

Topic	NICE recommendation	PhD contribution
Population	'Children and adults taking medicines for one or more clinical condition(s) in the UK'	The recommendation was partially implemented. There is insufficient clinical evidence on CMR carried out for children; therefore, modelling was not possible for that group. The populations included in the analyses were the general population of acutely hospitalised elderly in the short-term model (chapter 4) and hospitalised elderly with primary diagnosis of HF in the long-term model (chapter 6).
Intervention	'The study would need to take into account: the type of medication review carried out' (NICE, 2015a)	The recommendation was implemented by identifying comprehensive medication review (CMR) as the type of medication review used in the evaluation. CMR in chapters 4 and 6 was defined as 'any systematic assessment of the pharmacotherapy of an individual patient that aims to evaluate and optimise patient medication by a change in prescription either by a recommendation or by a direct change' (Christensen & Lundh, 2016). Moreover, study 6 further defines that the intervention used in the analysis was a CMR completed with STOPP/START criteria as a tool for determining the quality of prescribing.
Comparator	'Usual care or other interventions would be used as a comparator. Usual care would need to be defined in the study' (NICE, 2015a)	In both models the comparator is usual care, which was defined as: a medication review done inconstantly, low-quality medication review or ad hoc medication review and not a comprehensive medication review.

Outcomes	‘Outcomes for this research question should be patient-centred and include the suboptimal use of medicines, patient-reported outcomes, clinical outcomes, medicines-related problems, health and social care resource use and cost-effectiveness’ ‘The following outcomes should be considered: Medicines-related patient safety incidents, quality of life, clinical outcomes medicines-related problems (for example, medication errors) health and social care resource use.’ ‘Quality of life should be assessed using an EQ–5D questionnaire so that a cost-utility analysis can be conducted’ (NICE, 2015a)	The outcomes used in the model include: 1. Suboptimal use of medicines outcomes, measured as rate of potentially inappropriate prescribing (chapter 6) 2. Clinical outcomes and medicines-related problems: Chapter 6 • Mortality • Hospitalisation for three types of adverse drug events: exacerbation of HF, falls and hyponatremia Chapter 4 • Emergency Department reattendances averted 3. Health and social care resource use and cost-effectiveness: Chapters 4 and 6 • Cost of medicines • Cost of delivering CMR intervention Chapter 6 • Cost of hospitalisation and long-term care for patients with HF, including cost of treatment for exacerbation of HF, falls and hyponatremia Chapter 4 • Cost of Emergency Department reattendance 4. Quality of life Chapter 6 estimates the QALY gain from using CMR intervention. QALYs were calculated by attaching utilities to each Markov state and running the model. The utilities are based on EQ-5D questionnaires collected in different studies with a similar population and similar Markov health states. For the stable heart failure state, the utilities were calculated by a study that used the time trade-off method.

Study design	'Research can be carried out using an RCT. Study methodology can be based on other well-conducted RCTs that have been carried out looking at medication reviews' (NICE, 2015a)	Both the short-term model for general population presented in chapter 4 and the long-term cost-effectiveness model for HF population presented in chapter 6 use systematic literature reviews with meta-analyses of RCTs as the basis for the effectiveness of CMR (Christensen & Lundh, 2013, 2016; Hill-Taylor *et al*., 2016).
Time horizon	'A follow-up period of 1–2 years or more would capture longer-term outcomes' (NICE, 2015a)	The short-term cost-effectiveness model from chapter 4 was carried out with a 12-month time horizon. The long-term model from chapter 6 uses a lifetime horizon and it was for 300 cycles, which is equivalent to 25 years.

Source for recommendations: (NICE, 2015a)

Healthcare professional delivering CMR

In the Guidelines on Medicines Optimisation (NICE, 2015a), NICE recommends that the study should also focus on a cost-effectiveness analysis of CMR delivered by different healthcare professionals. The PhD addressed that gap in the literature by performing sensitivity analyses in chapter 4, in which parameters were adjusted to represent the cost-effectiveness of CMR delivered by different healthcare professionals. The PhD was the first study that looked at the health economic impact of CMR delivered by different healthcare professionals. It has strengthened the current recommendation of NICE by providing previously unavailable data. The recommendation is that the most appropriate healthcare professional to deliver the intervention should be determined locally.

In the PhD there was a good indication that pharmacist might be at the 'sweet spot' between having enough experience to deliver a good quality CMR and still being a cost-saving alternative. However, it is still up to local decision makers to decide on the most appropriate healthcare professional to deliver the intervention.

Estimating the impact of different types of healthcare professionals on the cost-effectiveness of CMR, which I have done in my study, can help local decision makers in allocating appropriate resources. Decision makers can use the results of the study in conjunction with their budget, availability of staff, experience of staff etc to determine who will deliver CMR in their local setting (please refer to 7.5 'Policy and practice implications' for more detail).

Target population for CMR

The PhD also contributes towards understanding which patients should receive CMR and how cost-effectiveness differs across different patient populations. The current recommendations by NICE suggest that CMR intervention should be delivered to patients on polypharmacy, the elderly and people with chronic conditions (NICE, 2015a). The population in the guidelines reflects all the patients that could need their medicines optimised. However, doing analyses for such a broad general population has many methodological disadvantages and the results of a cost-effectiveness analysis could be highly uncertain.

Because of that I created two analyses: one that looks at more uncertain estimates for the whole population that may receive CMR, and a second analysis for a more specified target population, which is narrower, but has the advantage of less uncertainty surrounding the findings. Modelling the cost-effectiveness of CMR for a general population of elder acutely hospitalised patients over a short timeframe (12-month time horizon) was carried out in chapter 4. Long-term cost-effectiveness modelling that also estimated the QALY gain from CMR was carried out for hospitalised HF elderly in the UK NHS. Chapter 4 indicated that CMR was potentially cost-saving for the general population over 12 months. The results for the HF population carried out over 25 years did not confirm that CMR is cost-saving, but it was still estimated that CMR was cost-effective, with ICER of £3,144 per QALY. The difference in results may reflect the different target population of each cost-effectiveness model, but it could also indicate that over a longer timeframe the costs of delivering the intervention increased.

Furthermore, a subgroup analysis was conducted in both studies. The findings suggest that CMR was a cost-effective option for all the age groups analysed beginning from patients aged ≥60. Lower age groups were not looked at in the analyses. The cost-effectiveness of CMR increased as the age of patients increased. In the study from chapter 6, the subgroup analyses were also conducted for different severities of HF measured by NYHA classification. The cost-effectiveness increased as the severity of HF decreased. The higher cost-effectiveness was a result of bigger QALY gain, because of increased quality of life of these patients and a longer life expectancy during which they can use CMR intervention.

Based on literature review and analyses of routinely collected data, chapter 5 identified the target population of patients that could benefit from CMR and described priorities for further economic exploration for the selected populations. As described above, cost-effectiveness of CMR was analysed for HF patients as part of this PhD thesis. The conditions which have public health importance and are associated with problematic polypharmacy can all be explored in further cost-effectiveness studies. Chapter 5 provides suggestions for other target populations that could be looked at, with COPD as the ideal candidate condition for further exploration of the economic effect of CMR.

Chapter 3 described a finding that indicated it might be possible that the effectiveness of CMR is different depending on gender. Results of the study showed that for age groups of 80-89-year-olds the CMR was more effective at reducing the overall polypharmacy burden among females. However, because the ReMAC study was not set up as an effectiveness study in order to test the hypothesis that CMR is more effective for females aged 80-89 compared to males of the same age, further research is required.

Setting in which medication review is delivered

The PhD provides previously unavailable information about the cost-effectiveness of CMR in the UK NHS hospital setting. The study is complementary with similar analyses conducted in other countries (Gallagher *et al*., 2016; Ghatnekar *et al*., 2013), which conclude that CMR compared to usual care is a cost-effective intervention in a hospital or long-term care setting. The only study in the literature with results which show CMR is not cost-effective in a hospital setting (Wallerstedt *et al*., 2012) concluded that the complexity of healthcare requires robust economic evaluations, rather than the simplistic interpretation of data done as part of that study.

Contrary to the results of my study and international literature about CMR in a hospital setting, five of six studies which looked at the economic evaluations of CMR conducted in a community setting concluded that CMR was not cost-effective or it was cost-incurring. This might suggest that CMR carried out in a hospital setting is more likely to be cost-effective compared to CMR carried out in a community setting. However, none of the studies of CMR delivered in a community setting looked beyond a 12-month time horizon. Early optimisation of medicines might potentially lead to patients not attending hospital in the first place. In addition, medicines optimised in hospital, but later changed in the community, can lead to readmission to hospital. Therefore, it is essential that medicines optimisation is an integrated process with appropriate communication between primary, secondary, community and social care.

7.2.2 Methodological contributions

Development of two de novo models of cost-effectiveness of CMR that can be used in further exploration of the economic impact of CMR

The current literature on economic evaluations of CMR is limited in the number of cost-effectiveness models available. Most of the current cost-effectiveness analyses are studies alongside RCTs. Therefore, the cost-effectiveness relates only to the population included in the study and the time horizon of the analysis is limited to the follow-up in the study. The studies are also based on a single RCT and do not incorporate all the available evidence. Because not all the relevant evidence is considered and results reflect only the RCT's population, results of the current studies are not consistent with each other.

Both models included in the PhD provide previously unavailable information about the cost-effectiveness of CMR in the UK NHS hospital and long-term care setting. They are also both based primarily on systematic literature review, uses evidence synthesis and decision analytic modelling.

Chapter 4 presents the decision tree model for the general population of acutely hospitalised elderly. The model was created to capture the costs associated with the intervention from a UK NHS perspective with a time horizon of 12 months. The model's structure starts with a decision node that indicates choice between CMR and usual care and this influences the probability of a patient avoiding emergency department reattendance. As mentioned before, CMR is a complex intervention and there are several factors that can differ depending on the local setting: the effectiveness of CMR, healthcare professionals delivering the intervention, time needed to complete the review, population of patients and costs. The advantage of this modelling approach is its simplicity, where all the above-mentioned parameters can be populated with data from local settings. The model can serve as a tool for local decision makers to analyse the cost-effectiveness of delivering CMR in their local context.

Chapter 6 describes the cost-utility analysis of CMR vs usual care for hospitalised HF patients in the UK NHS. The model is constructed in two complementary parts, a short-term decision tree model and a long-term Markov model. The decision tree

model looks at the immediate effect of CMR on prescribing during the initial hospitalisation for HF patients. There is a chance that patients will avoid a PIP or that the patient will receive a PIP. There are six PIPs that the patient might receive. Depending on the progress in the decision tree model, patients enter the model either without a PIP or with one of the six PIPs. All the states have a probability of moving from stable HF to dead state or having one of three possible adverse drug events: exacerbation of heart failure, fall or hyponatremia. The model is based on systematic literature reviews of RCTs and other evidence from the literature as well as routinely collected data in the form of Hospital Episode Statistics. The final outcome is Incremental Cost Effectiveness Ratio, based on health benefits, measured in QALYs, and costs. The model was constructed to look at patients with HF, however there is possibility to use a similar structure in other health conditions. If we know what the most common PIPs are in a given population and we know from the evidence base around STOPP/START criteria what the negative consequences of certain PIPs are, it is possible to replicate the study for a different population.

In summary, the methodological contribution of the two models is that they can serve for further economic exploration of CMR, either with local data for local context or with data for other target populations nationwide.

Methodological solutions for analysis of complex healthcare interventions (case study of CMR)

CMR is a complex healthcare intervention. The evaluation of CMR and methods used to evaluate it can serve as a case study for further exploration of complex interventions in healthcare. The methodological contributions in the aspect of evaluating complex interventions were made in chapters 2 and 6.

Chapter 2 is a literature review aimed at identifying articles describing the complexity of CMR. Framework analysis was conducted using the Institute of Health Economics (IHE) criteria (Husereau *et al*., 2014) to classify the complexity of hospital CMR. The challenges in evaluation of complex intervention (CMR) were identified for the following themes: valuing outcomes, comparators, perspective, resource use and costs, effectiveness and modelling. The study provides insight into how complex interventions differ from simple interventions and how that affects the methods used

in economic evaluations. Complex system interventions such as medication review are difficult to evaluate given the scope and number of factors to consider. When evaluating complex interventions using the standard health economic approach there are many challenges that the researcher needs to consider. Therefore, researchers can consider aspects of complexity and context dependencies when evaluating complex interventions.

Chapter 6 is a practical use of recommendations from chapter 2, where aspects of complexity were applied into a cost-effectiveness model of CMR. The complex nature of the problem and the current evidence available were not sufficient to implement all the recommendations. However, the cost-effectiveness study implemented the majority of the recommendations. The study proved that it is possible to use a traditional extra-welfarism theoretical framework to evaluate the cost-effectiveness of complex interventions such as CMR. The analysis used detailed modelling approaches and robust sensitivity analyses, but decision makers need to be mindful of the underlying assumptions about the mechanisms of effects that could influence the delivery of the intervention and system organisation that could not be easily tested in sensitivity analysis.

Not all complex interventions are created equal. Hence, further research is required to understand when it is possible to use traditional health economic methods and when a new approach should be implemented.

In conclusion, the methodological contributions relating to economic evaluation of complex interventions were made in chapters 2 and 6. Chapter 2 presents the framework and recommendations for conducting economic analyses of complex intervention (CMR) and chapter 6 is a practical use of the recommendations in an economic evaluation of complex intervention.

7.3 Key assumptions and limitations

Key assumptions and limitations were discussed at the end of each chapter for all five studies separately. For more information on limitations relating to a specific study design or modelling approach, please see the strengths and limitations

sections 2.4.3, 3.4.3, 4.4.3, 5.4.3 and 6.5.3. This section is intended to bring together and summarise the main assumptions and limitations of the thesis.

Below is a summary of the main assumptions used for economic modelling of CMR:

- The main benefit of CMR is deprescribing of PIPs (this was in line with findings from empirical study conducted in chapter 3).
- CMR is effective in reducing PIPs with an odds ratio of 2.98 (95% CI 1.30; 6.83) in favour of the CMR group (Hill-Taylor *et al*., 2016).
- PIPs lead to increased morbidity and mortality and the reduction of PIPs is used as an intermediate outcome to measure QALY gain from CMR (based on evidence from STOPP/START criteria (Gallagher, Ryan, Byrne, Kennedy & Mahony, 2008; O'Mahony *et al*., 2010; O'Mahony *et al*., 2015)).
- In the base-case analysis of the cost-effectiveness model it was assumed that CMR was pharmacist-led. Sensitivity analysis was used to test how the results changed if the cost of CMR was altered to represent other healthcare professionals delivering the intervention.
- CMR was assumed to be a 'structured critical examination of all current medication with the objective of reaching an agreement with the patient about treatment, considering the merits and risks of different medications, stopping inappropriate medicines and starting others, optimising their impact, minimising the number of medication-related problems and reducing waste' and in chapter 6 the tool for determining the quality of prescribing in CMR was assumed to be STOPP/START criteria (based on Szymanski *et al*., 2016 and Ward *et al*., 2019 and STOPP/START criteria (O'Mahony *et al*., 2015)).
- Usual care was assumed to be a medication review done inconstantly, low-quality medication review, ad hoc medication review or noncomprehensive medication review.
- The assumed prevalence of PIPs among patients comes from two studies: one study of patients with HF (Bermingham *et al*., 2014) found that 57.7% of patients met at least one STOPP/START criterion during their stay at the hospital; the second study used for modelling measured the prevalence of PIPs in the general population (Bradley *et al*., 2014), where 295,653 of 1,019,491 (29%) people aged 70 years or older had at least one PIP.

- Well-trained healthcare professionals can deliver high-quality CMR.
- The six most common PIPs, as measured by STOPP/START criteria, were used to represent the effect of deprescribing following CMR for patients with HF (based on study of PIPs among patients with HF (Bermingham *et al*., 2014) and STOPP/START criteria (O'Mahony *et al*., 2015)).
- The effects of CMR are sustained when patients are discharged from the hospital. This is based on a RCT (Frankenthal *et al*., 2014) where a follow-up trial after 24 months investigated whether the effects of the CMR were sustained (Frankenthal *et al*., 2017). The authors conclude that the effect of CMR using STOPP/START criteria was maintained over time.
- The baseline probability of patients 65 years or older reattending emergency department is 0.59 and comes from the national Hospital Episode Statistics (HES, 2012).
- CMR reduces emergency department contacts with an RR of 0.73 (95% CI 0.52; 1.03) (Christensen & Lundh, 2016).
- CMR was available to all hospitalised patients from the target population (chapter 4 – all acutely hospitalised NHS patients aged 65 years or older; chapter 6 – all patients hospitalised with heart failure over the age of 70).
- The additional time needed for a pharmacist to complete the CMR intervention was on average 33.6 minutes (95% CI 31.9 to 35.5) (Brodersen Lind *et al*., 2016) and it was estimated that the unit price of CMR was £25.20 (SE = 0.03).

Most of the assumptions mentioned above were tested through both deterministic and probabilistic sensitivity analyses. Even when values were modified significantly, where extreme values were tested (e.g. CMR was only 10% effective in reducing the number of PIPs or only 1% of the population had PIPs prescribed), CMR was still a cost-effective intervention. There were 10 probabilistic second-order Monte Carlo simulations conducted, each with different structural assumptions and each with 10,000 simulations. In all of them there was a 99% probability of CMR being cost-effective (both with £10,000 and £20,000 per QALY thresholds).

Thorough modelling and extensive sensitivity analyses provide confidence that CMR is cost-effective, but limitations still exist.

Economic evaluation of CMR is difficult because of the limitations of traditional health economic methods when applied to complex interventions. This is true for all complex interventions where, even if researchers carefully consider various aspects of complexity in their evaluations, it can never be completely disregarded in the analysis results. Cost-effectiveness analysis of CMR can have lower generalisability of results compared to cost-effectiveness analysis of a new drug, because of the context dependencies and because CMR can be tailored to the local setting.

Measuring the final health outcome of complex interventions carries with it a host of challenges:

1. Complexity of the intervention limits the study design in clinical trials
2. There is often limited data available due to complex interventions being unresearched
3. Often, the benefits of interventions are other than quality and length of life (the recommended gold standard for health economic evaluations).

These challenges to measuring the final outcome hold true for CMR, where an intermediate outcome of reducing PIPs was used to quantify the final health outcome of QALY gain. Decision makers need to be mindful of the underlying assumptions that could not be easily tested in a sensitivity analysis. Not all the assumptions could be tested because CMR is a complex intervention influenced both by having several interacting components and by the complexity of the system in which it is delivered. A health intervention can be simple or complicated, but when delivered in a complex system any intervention can become complex (Shiell, Hawe & Gold, 2008).

Systems are dynamic and there are many theories of systems that would be interesting to combine with cost-effectiveness analysis of CMR. However, this PhD focuses mainly on addressing the complex nature of the intervention, rather than of the wider healthcare system.

To account for the complexity of the intervention, I gave special consideration to the six aspects of complexity described by the Institute of Health Economics (Husereau *et al*., 2014) that require special attention when performing economic evaluation. In

chapter 2, I described the challenges of conducting economic evaluation of CMR, in relation to the complexity of CMR. In chapters 4 and 6, I applied recommendations from chapter 2 to the short- and long-term cost-effectiveness models of CMR. Complexity influences the generalisability of the results, therefore the economic evaluations of a complex intervention should be detailed when reporting the findings and assumptions. I provide a summary of key assumptions used in the thesis to allow decision makers to consider whether the assumptions used in the models meet their local and setting-specific requirements.

7.4 Further research

The studies presented as part of the PhD thesis outline key contributions to the research on the economic impact of CMR. The work done as part of the PhD also identifies areas that require further exploration. I will briefly highlight five key research areas.

1. **Evaluation of complex intervention and complex systems**

Firstly, future research could focus on exploration of different methods for evaluation of both effectiveness and cost-effectiveness of complex intervention and complex systems. The current guidelines in this area are scarce and require further systematisation. Furthermore, the current guidelines can be limited to one field of focus of the complex interventions, instead of looking at the complexity science holistically. The guidelines relate to fields such as: public health, integrated and community care services, electronic health technologies, interventions in operating theatres etc. There is a need for integration and a broader look at complexity in healthcare. Interventions delivered in complex systems like primary care or hospitals or public health interventions can be simple or complicated. Because they can be influenced by behaviours and the context in which they are delivered, they can all be complex interventions (Shiell *et al*., 2008). Chapter 2 of the PhD explains why CMR can be classified as a complex intervention and how that influences the cost-effectiveness analysis of CMR. There are more case studies required to expand the current knowledge about different methods required for economic evaluation of complex interventions. A study conducted as part of chapter 6 showed that with detailed modelling and making the right assumptions it is possible to use a traditional

extra-welfarism theoretical framework to evaluate the cost-effectiveness of complex interventions. Further research can focus on understanding how and when it is possible to use traditional economic evaluations and when other methodological approaches should be implemented.

2. Cost-effectiveness of implementation strategies and quality improvement

A second key area of future research could be economic evaluations of implementation strategies and quality improvement. There are many examples where healthcare improvement initiatives and quality improvement have impacted care for patients nationwide (Davidson *et al*., 2017; Farr *et al*., 2018; Ferrer *et al*., 2018; Ham, Berwick & Dixon, 2016; Linertová, García-Pérez, Vázquez-Díaz, Lorenzo-Riera & Sarría-Santamera, 2011; NHS Employers, 2017; Ravesloot, Seekins & White, 2005; Soric, Glowczewski & Lerman, 2016; Stringer *et al*., 2006; The Health Foundation, 2013; Trzeciak *et al*., 2006; Zangaro & Soeken, 2017). The resources needed for improvement work can be highly underestimated, which can lead to failure of the initiative and can impact on its costs. The future of quality improvement is dependent on improving our understanding of how to achieve and reproduce improvement efforts in diverse settings. There is limited research that quantifies the work, effort, resource and time needed to achieve improvement in complex systems. Chapter 3 describes the findings from the ReMAC study, a multicentre implementation study with a 15-month follow-up. The studies conducted as part of this PhD suggest that it is highly likely that CMR is a cost-effective intervention, but findings from the ReMAC study show that before the implementation initiative started, the average number of reported CMRs was just 4%. The implementation initiative resulted in an increase of reported CMRs to 63%. Further research could focus on estimating the cost-effectiveness of an implementation initiative designed to improve the uptake of CMR. In order to do that, resources and contributing factors need to be correctly identified. Once identified, the overall cost of these activities should be estimated by creating an algorithm for a bottom-up costing.

3. Economic evaluation of interventions optimising healthcare/prescribing

The third recommendation for an area of research is to conduct further evaluations of existing interventions aimed at improving prescribing quality or improving general service delivery in healthcare. Currently, economic analyses focus more on adding additional health technologies to the market, but these technologies can strain the already limited healthcare budget and add more obligations for healthcare professionals.

Medicines optimisations interventions such as medication review provide an example of existing health technologies already available in the NHS, albeit with suboptimal quality and consistency of delivery. Even though the studies from chapters 3, 4 and 6 show that the interventions aimed at optimising prescribing can be cost-effective, the suboptimal delivery of these interventions can impact on other existing treatments and on the effectiveness and safety of medicines which are prescribed to patients. Medicines which are inappropriately prescribed can provide more harm than intended benefit. This impacts on the costs and health effects for patient who receive such inappropriately prescribed medicines.

The reason that many cost-effective interventions are not widely used across the healthcare system is associated with barriers to improvement. In its research, The Health Foundation has recognised four key barriers to achieving successful improvement in the NHS:

- Initiative-related barriers (usability of interventions; insufficient evidence base; fitting the process).
- Individual (staff resistance to change; skills and knowledge).
- Organisational (organisation culture; lack of leadership; time constraints; insufficient use of data; management and funding)
- System-wide barriers (political and financial instability; NHS culture; partnerships; funding).

(de Silva, 2015; Solomons & Spross, 2011)

Properly implemented quality improvement initiatives such as those described in the ReMAC study in chapter 3 can overcome the barriers to achieving improvement in healthcare.

Therefore, further research could focus on the economic impact of other medicines optimisation interventions, which can also serve as case studies for cost-effectiveness of implementation strategies and QI projects (research area number 2).

4. **In-depth analysis of CMR intervention (cost of started medicines and gender impact on the effectiveness of CMR)**

Although this PhD highlighted key aspects of effectiveness, cost-effectiveness and implementation of CMR, there are still areas that could not be addressed within the timeframe of this PhD.

Because of low availability of data about cost of started medicines in the ReMAC study in chapter 3, I could not accurately determine the difference in cost of started medicines between the CMR and usual care groups. The lack of follow-up in the data also prevented me from analysing how these costs develop over time. Future research could attempt to estimate the difference in cost of started medicines between CMR and usual care groups. This would allow for more accurate estimation of the direct costs of medicines between the two groups.

A second research recommendation also came out of chapter 3. The PhD research found that for women, age did not make a difference in terms of the effectiveness of CMR, but for men between 80 and 89 years old, age was a factor that influenced the difference between medicines on discharge and medicines on admission. The ReMAC initiative was not designed for evaluation of the effectiveness of CMR because this was not a randomised control trial or a cohort study and there was no blinding. This could impact on the selection and allocation bias, because the design of the study was a quality improvement initiative. Therefore, in order to see how change impacts the effectiveness of CMR and whether for certain age groups CMR is more effective for women, a confirmatory experimental trial needs to be conducted.

5. Cost-effectiveness of CMR for other populations and different context

The final priority for research is further exploration of CMR for different populations and different settings. Chapter 4 was a cost-effectiveness analysis of CMR in the general population, but over a short timeframe. Chapter 6 looked at long-term cost-effectiveness of CMR, but just for patients with HF. There is a need to look at other populations of patients and explore the economic impact of CMR on these patients.

The research could focus on finding the 'limit' at which the CMR is no longer cost-effective. The case selected as part of this PhD indicated an area in which CMR could be most cost-effective. Focusing research on populations and settings in which CMR might provide less value for money could help us understand at what point CMR stops being cost-effective and what determines why it is cost-effective in one area but not in the other.

The other focus for cost-effectiveness analysis could be one of the other high impact populations identified in chapter 5, such as COPD. COPD met all the requirements to be considered an important population on which to focus research effort. COPD is a chronic care condition that can be characterised as a population of high public health importance as it is responsible for 2.95% of all in-hospital mortality (NHS Digital, 2018d) and has a high emergency admission rate of 2.48% of all emergency admissions (Aylin *et al*., 2010). COPD has high readmission rates of 10.2% to 28.0% (Bottle, Honeyford, *et al*., 2018; Demir *et al*., 2008; Friebel *et al*., 2018; Harries *et al*., 2017; Hekkert *et al*., 2018; Morton *et al*., 2019; Steer *et al*., 2012) and a high economic burden of between £928 million and £3,532 million per year (Britton, 2003; McLean *et al*., 2016; NHS Medical Directorate, 2012; Trueman *et al*., 2017). Patients with COPD experience problematic polypharmacy and as a result the chance of having at least one PIP prescribed is between 25% and 54% (Bradley *et al*., 2014; Komagamine, 2018; Rothberg *et al*., 2008; Vezmar Kovačević *et al*., 2014; Wawruch *et al*., 2008).

CMR is a complex intervention and can be delivered in various settings: community (GP practices, patients' homes, community pharmacies etc), hospitals, acute care, nursing homes etc. Studies of CMR done in a community setting have estimated that

CMR was not cost-effective in that setting, however the time horizon for all studies did not exceed 12 months. There is a need for robust economic evaluation using economic modelling to look at the cost-effectiveness of CMR beyond 12 months. Early optimisation of medicines might lead to reduced admission to hospital, thus avoiding the initial acute hospitalisation.

Different healthcare professionals can deliver CMR and there are different tools (e.g. STOPP/START criteria, Beers criteria etc) that facilitate the delivery of the intervention. There are also different ways in which CMR can be delivered (e.g. during ward rounds or via written or oral communication of recommendations to other healthcare professionals), different types of reconciliation of medicines and different patient records used for CMR. All the complexity may in fact suggest that there is not one but many different types of CMR. Future research could focus on conducting an economic analysis of all different types of CMR.

7.5 Policy and practice implications

The study showed that CMR done in a hospital setting is a cost-effective option compared to usual care in the UK NHS for patients with HF in the long-term timeframe. There are indications that CMR also has the potential to be a cost-effective intervention for the general population of patients. The findings can impact on both policy and practice.

Policy implications

The NICE Guidelines on Medicines Optimisation (NICE, 2015a) recommend conducting CMR. However, evidence on the cost-effectiveness of CMR in a hospital setting comes from outside of the UK and is mostly set up as studies alongside a RCT, instead of modelling studies (see section 1.4 ‘Gaps in the literature and rationale for the PhD’ for information on limitations of the current evidence). The study carried out as part of the PhD addresses these gaps in the literature and provides new evidence based on UK-specific data and modelling of evidence from meta-analysis of RCTs. The cost-effectiveness analyses of CMR conducted as part of this PhD can be used in the future to update the NICE guidelines.

Another area in which this study can impact on policy is the recommendation that the PhD makes about investing in implementation initiatives to increase the uptake of CMR. The PhD showed that there is a 99% probability that CMR is cost-effective; the additional cost of delivering CMR is very low compared to the health benefits it can deliver. However, the ReMAC study presented in chapter 3 highlights that before implementing the quality improvement initiative, the uptake of CMR was very low (4% of all eligible patients). After 15 months of implementing the 'breakthrough collaborative' initiative, the average rate of documented CMRs increased to 63%. Because it is estimated that CMR is cost-effective, it is very likely that investing additional funds for implementation of CMR would still be beneficial and cost-effective. For that to happen, additional research is required into the resources and effort needed to achieve successful implementation of a complex intervention in the healthcare system (see 7.4 'Further research' for recommendations).

Practice implications

The PhD can influence practice by allowing local organisations and commissioners to determine their own value for money of CMR. NICE guidelines (NICE, 2015a) highlight that CMR is very much influenced by local context; it can be delivered by different types of healthcare professionals in different settings. NICE highlights that research into resources (e.g. cost of delivering CMR, time needed to deliver the intervention, type of healthcare professional) can provide guidance to local organisations that deliver CMR and can facilitate service delivery (NICE, 2015a). The commissioners also need that information in order to make decisions should they commission CMR in their local CCG. Almost all chapters in the PhD provide information that can help influence the local decisions and improve current practice.

Chapter 3 provides evidence on how to deliver a successful implementation initiative of CMR and describes positive effects of CMR on prescribing patterns. Chapters 4 and 6 are cost-effectiveness models that can be populated with local data from hospitals or CCGs in order to determine whether CMR is also cost-effective at a local level. The chapters provide information on how cost-effective CMR is when delivered by different healthcare professionals. Based on the type of healthcare professional delivering CMR locally, decision makers can see how cost-effective the CMR will be in their local context (see chapter 4, section 4.3.3 'Deterministic sensitivity analysis').

The cost of CMR and time needed to complete the intervention is also estimated in the cost-effectiveness models. In terms of cost it was estimated that the unit price of pharmacist-led CMR in the UK NHS is £25.20 (95% CI; £23.90-£26.60). This can of course differ in the local context, but can be easily calculated based on the type of healthcare professional delivering CMR and the time needed to complete the intervention. Time needed to complete CMR used in the model is based on the (Brodersen Lind *et al*., 2016) study, which estimated that on average it took 33.6 minutes (95% CI 31.9 to 35.5) to complete a CMR. The sensitivity analysis conducted in chapter 4 determined that CMR which is delivered within 33 minutes can even be cost-saving; if it is over 33 minutes it can still be cost-effective depending on the cost-effectiveness threshold.

Finally, the study in chapter 5 and sensitivity analysis in chapters 4 and 6 describe target populations of patients that can receive CMR. The subgroup analysis in the cost-effectiveness models can also help with prioritisation of patients that should always receive the intervention.

In conclusion, the results from the PhD can impact on policy directions and future investments in providing CMR intervention. The PhD also impacts practice and can facilitate local decision makers to provide high-quality CMR. In combination, investment in implementation and ease to determine locally what the cost-effectiveness of CMR is can increase the number of CMRs delivered.

7.6 Conclusions

This economic evaluation conducted as part of this PhD suggests that CMR is likely to be cost-effective in eligible patients with HF in a long-term timeframe from the UK National Health Service (NHS) and personal social services (PSS) perspective. The cost-effectiveness of CMR for the general population is most likely to be cost-saving in the short timeframe from the UK NHS perspective.

CMR is a complex healthcare intervention that can be conducted in multiple settings and by different healthcare professionals; therefore, its effectiveness and cost-effectiveness is likely to depend on behavioural factors and contextual factors.

Thus, it is important to try to account for context and complexity when evaluating effectiveness and cost-effectiveness of CMR.

CMR can be conducted for different groups of patients. The target group may include heart failure and COPD patients as both are chronic conditions with recognised morbidity and mortality and are a common reason for emergency admission and readmission to hospital. Patients with HF and COPD are at risk of problematic polypharmacy and potentially inappropriate prescribing and these conditions are often associated with comorbidities. These conditions can lead to high financial pressure on the NHS due to their high use of NHS hospitals and resources.

Analysis of data from an empirical study done at five hospitals in North West London showed that CMR compared to usual care reduced the overall polypharmacy burden through increased deprescribing of medicines. This resulted in a statistically significant lower difference between the number of medicines on discharge and at admission for the CMR group compared to the usual care group. CMR resulted in cost-savings from deprescribing medicines and thus empirical study results complement the findings from both cost-effectiveness models.

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APPENDIX A EMERGENCY MEDICINE INVESTIGATION AND TREATMENT CODES

Table A Healthcare Resource Groups (HRGs) reference costs grouper codes for emergency medicine investigation and treatment

EM Code Type	EM Code	EM Code Description
Invest	01	X-ray plain film
Invest	02	Electrocardiogram
Invest	03	Haematology
Invest	04	Cross match blood/group and save serum for later cross match
Invest	05	Biochemistry
Invest	06	Urinalysis
Invest	07	Bacteriology
Invest	08	Histology
Invest	10	Ultrasound
Invest	11	Magnetic Resonance Imaging
Invest	12	Computerised Tomography (excludes genito urinary contrast examination/tomography)
Invest	13	Genito urinary contrast examination/tomography
Invest	14	Clotting studies
Invest	15	Immunology
Invest	16	Cardiac enzymes
Invest	17	Arterial/capillary blood gas
Invest	18	Toxicology
Invest	19	Blood culture
Invest	20	Serology
Invest	21	Pregnancy test
Invest	22	Dental investigation
Invest	23	Refraction, orthoptic tests and computerised visual fields
Invest	24	None
Invest	99	Other
Treat	011	Dressing minor wound/burn/eye

Treat	012	Dressing major wound/burn
Treat	02	Bandage/support
Treat	031	Primary sutures
Treat	032	Secondary/complex suture
Treat	033	Removal of sutures/clips
Treat	041	Wound closure - steristrips
Treat	042	Wound closure - wound glue
Treat	043	Wound closure - other (e.g. clips)
Treat	051	Application Plaster of Paris
Treat	052	Removal Plaster of Paris
Treat	06	Splint
Treat	08	Removal foreign body
Treat	091	Physiotherapy - strapping, ultrasound treatment, short wave diathermy, manipulation
Treat	092	Physiotherapy - gait re-education, falls prevention
Treat	101	Manipulation of upper limb fracture
Treat	102	Manipulation of lower limb fracture
Treat	103	Manipulation of dislocation
Treat	11	Incision and drainage
Treat	12	Intravenous cannula
Treat	13	Central line
Treat	14	Lavage/emesis/charcoal/eye irrigation
Treat	15	Intubation and endotracheal tubes/laryngeal mask airways/rapid sequence induction
Treat	16	Chest drain
Treat	17	Urinary catheter/suprapubic
Treat	181	Defibrillation
Treat	182	External pacing
Treat	19	Resuscitation/cardiopulmonary resuscitation
Treat	20	Minor surgery
Treat	21	Observation/electrocardiogram, pulse oximetry/head injury/trends
Treat	221	Guidance/advice only - written

Treat	222	Guidance/advice only - verbal
Treat	231	Anaesthesia - general anaesthetic
Treat	232	Anaesthesia - local anaesthetic
Treat	233	Anaesthesia - regional block
Treat	234	Anaesthesia - entonox
Treat	235	Anaesthesia - sedation
Treat	236	Anaesthesia - other
Treat	241	Tetanus - immune
Treat	242	Tetanus - tetanus toxoid course
Treat	243	Tetanus - tetanus toxoid booster
Treat	244	Tetanus - human immunoglobulin
Treat	245	Tetanus - combined tetanus/diphtheria course
Treat	246	Tetanus - combined tetanus/diphtheria booster
Treat	25	Nebuliser/spacer
Treat	27	Other (consider alternatives)
Treat	281	Parenteral thrombolysis - streptokinase parenteral thrombolysis
Treat	282	Parenteral thrombolysis - recombinant - plasminogen activator
Treat	291	Other Parenteral drugs - intravenous drug, e.g. stat/bolus
Treat	292	Other Parenteral drugs - intravenous infusion
Treat	30	Recording vital signs
Treat	31	Burns review
Treat	32	Recall/x-ray review
Treat	33	Fracture review
Treat	34	Wound cleaning
Treat	35	Dressing/wound review
Treat	36	Sling/collar cuff/broad arm sling
Treat	37	Epistaxis control
Treat	38	Nasal airway
Treat	39	Oral airway
Treat	40	Supplemental oxygen
Treat	41	Continuous positive airways pressure/nasal intermittent positive pressure ventilation/bag valve mask

Treat	42	Arterial line
Treat	43	Infusion fluids
Treat	44	Blood product transfusion
Treat	45	Pericardiocentesis
Treat	46	Lumbar puncture
Treat	47	Joint aspiration
Treat	48	Minor plastic procedure/split skin graft
Treat	49	Active rewarming of the hypothermic patient
Treat	50	Cooling - control body temperature
Treat	511	Medication administered - oral
Treat	512	Medication administered - intra-muscular
Treat	513	Medication administered - subcutaneous
Treat	514	Medication administered - per rectum
Treat	515	Medication administered - sublingual
Treat	516	Medication administered - intra-nasal
Treat	517	Medication administered - eye drops
Treat	518	Medication administered - ear drops
Treat	519	Medication administered - topical skin cream
Treat	521	Occupational Therapy - OT functional assessment
Treat	522	Occupational Therapy - OT activities of daily living equipment provision
Treat	53	Loan of walking aid (crutches)
Treat	54	Social work intervention
Treat	551	Eye - orthoptic exercises
Treat	552	Eye - laser of retina/iris or posterior capsule
Treat	553	Eye - retrobulbar injection
Treat	554	Eye - epilation of lashes
Treat	555	Eye - subconjunctival injection
Treat	56	Dental treatment
Treat	57	Prescription\medicines prepared to take away
Treat	99	None (consider guidance/advice option)

(NHS Digital, 2018b)

APPENDIX B SEARCH STRATEGY FOR LITERATURE REVIEW IN CHAPTER 5

Table B Search strategy for the literature review of economic burden, readmission rates and PIP rates for 10 CCS diagnostic groups with the highest public health impact.

Search	Query	Items found
#31	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	921
#30	Search ((((("septicaemia"[All Fields] OR "sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "septicemia"[All Fields]))))) AND ((beers criteria) OR stopp start)	0
#29	Search ((((Acute[All Fields] AND ("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields])))))) AND ((beers criteria) OR stopp start)	0
#28	Search (((((((("gastrointestinal hemorrhage"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "hemorrhage"[All Fields]) OR "gastrointestinal hemorrhage"[All Fields] OR ("gastrointestinal"[All Fields] AND "bleeding"[All Fields]) OR "gastrointestinal bleeding"[All Fields])))) OR (("gastrointestinal haemorrhage"[All Fields] OR "gastrointestinal hemorrhage"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "hemorrhage"[All Fields]) OR "gastrointestinal hemorrhage"[All Fields])))))) AND ((beers criteria) OR stopp start)	6
#27	Search ((((((("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields])))) OR (("femoral neck fractures"[MeSH Terms] OR ("femoral"[All Fields] AND "neck"[All Fields] AND "fractures"[All Fields]) OR "femoral neck fractures"[All Fields] OR ("fracture"[All Fields] AND "neck"[All Fields] AND "femur"[All Fields]) OR "fracture of neck of femur"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields])))))) AND ((beers criteria) OR stopp start)	14

Search	Query	Items found
#26	Search (((((("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields])) OR (Acute[All Fields] AND ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]))) OR ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields] OR ("heart"[All Fields] AND "attack"[All Fields]) OR "heart attack"[All Fields])))))) AND ((beers criteria) OR stopp start)	12
#25	Search ((((("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields]))))) AND ((beers criteria) OR stopp start)	5
#24	Search (((((Acute[All Fields] AND ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields]) OR "cerebrovascular disorders"[All Fields] OR ("cerebrovascular"[All Fields] AND "disease"[All Fields]) OR "cerebrovascular disease"[All Fields])))))) AND ((beers criteria) OR stopp start)	0
#23	Search (((((("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields])))))) AND ((beers criteria) OR stopp start)	8
#22	Search (((((((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields])))))))) AND ((beers criteria) OR stopp start)	11
#21	Search (((((((("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])))))))) AND ((beers criteria) OR stopp start))	28
#20	Search (((((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]))))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK	32

Search	Query	Items found
#19	Search (((((("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields]))))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK	8
#18	Search (((((("septicaemia"[All Fields] OR "sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "septicemia"[All Fields])))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK	4
#17	Search ((((((Acute[All Fields] AND ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields]) OR "cerebrovascular disorders"[All Fields] OR ("cerebrovascular"[All Fields] AND "disease"[All Fields]) OR "cerebrovascular disease"[All Fields])))))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK)	3
#16	Search (((((("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields])))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK	0
#15	Search (((((((("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields]))) OR (("femoral neck fractures"[MeSH Terms] OR ("femoral"[All Fields] AND "neck"[All Fields] AND "fractures"[All Fields]) OR "femoral neck fractures"[All Fields] OR ("fracture"[All Fields] AND "neck"[All Fields] AND "femur"[All Fields]) OR "fracture of neck of femur"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields])))))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK	7
#14	Search (((((((("gastrointestinal hemorrhage"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "hemorrhage"[All Fields]) OR "gastrointestinal hemorrhage"[All Fields] OR ("gastrointestinal"[All Fields] AND "bleeding"[All Fields]) OR "gastrointestinal bleeding"[All Fields]))) OR (("gastrointestinal haemorrhage"[All Fields] OR "gastrointestinal hemorrhage"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "hemorrhage"[All Fields]) OR "gastrointestinal	5

Search	Query	Items found
	hemorrhage"[All Fields])))))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK	
#13	Search (((((Acute[All Fields] AND ("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields])))))) AND (((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND UK	0
#12	Search (((((re admission*[Title]) OR re-admission*[Title]) OR readmission*[Title])) AND ((((("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])))))) AND UK	35
#11	Search ((((((readmission*[Title]) OR re-admission*[Title]) OR re admission*[Title])) AND ((((("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields])) OR (Acute[All Fields] AND ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]))) OR ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields] OR ("heart"[All Fields] AND "attack"[All Fields]) OR "heart attack"[All Fields]))) AND UK)	13
#10	Search ((((("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields])) AND ((cost[Title]) OR economic[Title])) AND UK)	68
#9	Search (((((cost*[Title]) OR economic*[Title])) AND ((((("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields])) OR (Acute[All Fields] AND ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]))) OR ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields] OR ("heart"[All Fields] AND "attack"[All Fields]) OR "heart attack"[All Fields]))) AND UK)	160
#8	Search (((((((("gastrointestinal hemorrhage"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "hemorrhage"[All Fields]) OR "gastrointestinal hemorrhage"[All Fields] OR ("gastrointestinal"[All Fields] AND "bleeding"[All Fields]) OR "gastrointestinal bleeding"[All Fields]))) OR (("gastrointestinal haemorrhage"[All Fields] OR "gastrointestinal	16

Search	Query	Items found
	hemorrhage"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "hemorrhage"[All Fields]) OR "gastrointestinal hemorrhage"[All Fields]))))) AND ((economic*[Title]) OR cost*[Title])) AND UK)	
#7	Search ((((Acute[All Fields] AND ("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields])))) AND ((economic*[Title]) OR cost*[Title])) AND UK)	6
#6	Search (((((economic*[Title]) OR cost*[Title])) AND ((((("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields]))) OR (("femoral neck fractures"[MeSH Terms] OR ("femoral"[All Fields] AND "neck"[All Fields] AND "fractures"[All Fields]) OR "femoral neck fractures"[All Fields] OR ("fracture"[All Fields] AND "neck"[All Fields] AND "femur"[All Fields]) OR "fracture of neck of femur"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields])))) AND UK)	82
#5	Search ((((("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields])) AND ((cost[Title]) OR economic[Title])) AND UK)	26
#4	Search ((((Acute[All Fields] AND ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields]) OR "cerebrovascular disorders"[All Fields] OR ("cerebrovascular"[All Fields] AND "disease"[All Fields]) OR "cerebrovascular disease"[All Fields])))) AND ((cost[Title]) OR economic[Title])) AND UK)	34
#3	Search ((((("septicaemia"[All Fields] OR "sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "septicemia"[All Fields])) AND ((cost[Title]) OR economic[Title])) AND UK)	46
#2	Search (((((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields])) AND UK) AND ((cost[Title]) OR economic[Title]))))	110

Search	Query	Items found
#1	Search (((((("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])))) AND ((economic*[Title]) OR cost*[Title])) AND UK)	182

APPENDIX C CLAHRC NWL STUDY PROTOCOL

Evaluation of the NIHR CLAHRC NWL Systematic Approach to translating evidence-based research into practice in healthcare

Research Protocol Version 6.0 8th February 2017

This protocol describes the study 'Evaluation of the NIHR CLAHRC NWL Systematic Approach' and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Study Management Group

Chief Investigator: Prof. Derek Bell

Co-investigators: Dr. Julie Reed
Dr. Laurel Issen
Dr. Tom Woodcock
Dr. Alan Poots
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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
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Funders

The National Institute for Health Research
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Richmond House
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SW1A 2NS

The Health Foundation
90 Long Acre
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WC2E 9RA

Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Related Documentation

This Protocol links to the following documents:
Information Sheet version 4.0
Group 4 Information Sheet version 1.0
General Consent Form version 1.0

Project Lead Consent Form version 2.0
Ethics IRAS 188851

Background

While peer-reviewed clinical evidence (such as journal articles, guidelines, toolkits) describe activities that healthcare providers can undertake to improve healthcare, they rarely come with a blueprint for how it can be embedded in routine practice.(Bate & Robert, 2002; Hoffmann *et al*., 2014; Kitson, Harvey, & McCormack, 1998; Shojania & Grimshaw, 2005).

The NIHR CLAHRC NWL programme has developed a systematic approach consisting of additional tools and methods to help with this process of embedding research into routine practice in healthcare. NIHR CLAHRC NWL funds and supports Quality Improvement Teams consisting of multidisciplinary staff (such as managers, doctors, nurses, pharmacists, and physiotherapists) and patients to use the systematic approach in projects lasting a fixed term e.g. 12 or 18 months.

The systematic approach includes activities which are proposed to provide benefits in the evidence translation process and are based on recommendations from existing research in this field (Bate & Robert, 2002; Langley *et al*., 2009; Shojania & Grimshaw, 2005). The approach includes strategies to support the planning, conduct and evaluation of evidence-translation efforts, and provides guiding principles for teams to work towards including the strategic principles to act scientifically and pragmatically, embrace complexity, and to engage and empower those responsible for and effected by translation efforts including frontline healthcare staff and patients. In addition the approach specifies a number of tools and methods to guide team progress. For example, one activity is known as process mapping, whereby Quality Improvement Teams collaborate to produce a diagram depicting standard procedures of care delivery. This is hypothesized to help the team to better understand their system and opportunities for intervention, as well as providing an opportunity for patients and multi-disciplinary staff to interact in different ways and empathize with each other’s perspectives (Langley *et al*., 2009).

The purpose of this research study is to thoroughly assess the strengths and weaknesses of the systematic approach and its component parts, and to better understand “what actually happens” during the process of evidence translation and improvement.

The research will be conducted through a series of 1:1 interviews and observations of group meetings and workshops with a diverse group of people involved in delivering and improving healthcare. This will include NHS doctors, managers, nurses, allied health professionals, data analysts, and commissioners, as well as academic researchers and members of the public. Documents produced in preparation for and as a result of these meetings will also be analysed. These methods will help to determine the strengths and weaknesses of the CLAHRC NWL approach to translate research into routine healthcare improvements.

The results of this research will be used to iteratively develop the approach and scale up improvements nationally and internationally.

While new clinical research is always necessary, much more needs to be done to apply existing research evidence more effectively in everyday practice. Therefore, this research project chooses to investigate the process of translating of research into healthcare practice.

CLAHRC NWL has worked with partners to identify priority areas for improving care in Northwest London. The Delivery themes are targeted at areas of high morbidity with high health and care related costs that are recognised areas for improvement within Northwest London. These include Breathlessness, Early Years and Frailty as areas where local data suggest there is scope to significantly improve quality and value of care.

The Cross-cutting themes draw on existing literature and build on the CLAHRC NWL experience enriching understanding of the complexity of translation. To support successful and sustainable outcomes it is necessary to:

- Embed: Maximise knowledge of staff and patients to understand processes of care to help ‘fit’ research evidence. Test changes using an iterative approach to allow teams to react to obstacles and opportunities.

- Engage: Establish meaningful dialogue between patients and healthcare providers to ensure that changes to practice are aligned with patient needs and priorities.
- Consider the whole person: Focus on both mental and physical wellbeing to ensure patient centred care and high value service design.
- Utilise information: Identify key priorities to target research and resources. Provide regular feedback on implementation progress and impact on patient health.
- Collaborate: Engage staff, academics and patients to develop shared consensus on how to approach implementation, measure outcomes and build collective ownership and commitment to deliver improvements.

The research priority is to thoroughly assess the strengths and weaknesses of the overall systematic approach and its component parts and use our findings to scale up and spread successful aspects of the work.

This research will be undertaken at project, theme and programme level using our academic partners' expertise in clinical sciences, improvement science, epidemiology and social sciences. This work will be both formative, with frequent feedback of research to aid the development of programme activities, and summative, leading to dissemination through peer-reviewed publications and conferences.

Research Questions

Primary Research Question

What are the strengths and weaknesses of the systematic approach in enabling and empowering Quality Improvement projects to deliver sustainable healthcare improvements in collaboration with multi-professional stakeholders including patients and the public?

Secondary Research Questions

Factors influencing fidelity of use and outcomes of using the systematic approach:

- How effectively are Quality Improvement methods and the systematic approach applied in Quality Improvement Projects, what contextual factors affect this and how can practice be improved?
- How does the use of the CLAHRC NWL systematic approach including quality improvement methods influence Quality Improvement project development and success?
- What are the strengths and weaknesses of the long-term success tool (part of the systematic approach) in supporting Quality Improvement projects to plan for sustainable, long term success beyond the end of project funding?
- How can the value of participating in Quality Improvement projects be measured for patients, staff, and organisations, both in terms of intended and unintended benefits?
- What are the strengths and weaknesses in the 4PI tool (part of the systematic approach) in supporting Quality Improvement projects to effectively engage patients and the public in the evidence translation process and healthcare improvements? This will include the following PhD projects:
    - Ms. Laura Lennox: use of the Long Term Success Tool, one component of the Systematic Approach. Supervisors: Prof. Derek Bell, Dr. Julie Reed
    - Mr. David Sunkersing: use of the systematic approach and outcomes in care planning for the elderly. Supervisors: Prof. Derek Bell, Dr. Julie Reed
    - Mr. Tomasz Szymanski: health economic outcomes of using the systematic approach in a case study aimed to improve pharmacy record-keeping. Supervisors: Prof. Derek Bell, Dr. Julie Reed
    - Ms. Sophie Spitters: use of the systematic approach and outcomes in a case study aimed to improve paediatric allergy services. Supervisor: Dr. Julie Reed, Professor John Warner
    - Ms. Federica Amati: use of the systematic approach and outcomes in a case study aimed to improve mental health services. Supervisor: Prof. Derek Bell

Engagement, facilitation, and training in methods and tools in the systematic approach:

- How effective is CLAHRC NWL at engaging people in the use of the systematic approach and in facilitating and teaching Quality Improvement teams to use it effectively?
- This research will be undertaken by Dr. Laurel Issen, Dr Catherine French, and Mr. Vimal Sriram.

Exploration of contextual factors and perspectives of groups and individuals in the evidence translation process:

- How can individuals, organisations, professional groups, and other communities contribute to the process of improving care and translating evidence into practice? What are the strengths and weaknesses in the systematic approach for enabling this to happen?
- What are the barriers and facilitators to support transfer of knowledge and acceleration of implementation as projects scale up and roll out to new settings?
- What are the strengths and weaknesses in the systematic approach in enabling cooperation and collaboration among diverse stakeholders including patients and the public?
- What does 'value' in healthcare mean for patients and healthcare practitioners? This will include the following PhD projects:
    - Ms. Meerat Kaur: Exploration of contextual factors and perspectives of groups and individuals in the evidence translation process, from the perspective of patient and public engagement and involvement. Supervisors: Prof. Derek Bell, Dr. Julie Reed
    - Ms. Izaba Younis: Exploration of contextual factors and perspectives of groups and individuals in the evidence translation process, from the perspective of exploring the value systems of different professional groups and the benefits they emphasize about involvement in Quality Improvement work. Supervisor: Prof. Derek Bell

Values

The research in this study utilizes an ‘action research’ methodology which is designed as an iterative process of action, reflection, and improvement, with the ultimate purpose of developing a systematic way to enable improvement. This means researchers will support Quality Improvement projects by communicating their findings with projects at short intervals and may be involved in close working relationships with these teams. For example, a researcher investigating the use of the Long-Term Success tool in one team may then use those findings to feed back to the team under investigation and to deliver training to other teams.

Participant Entry

There are four groups under investigation, which will have different methods of recruitment:
Group 1 will be Quality Improvement Project Teams funded by NIHR CLAHRC NWL,
Group 2 will be Individual Quality Improvement Fellows funded by NIHR CLAHRC NWL.
Group 3 will be individuals who are already in professional contact with NIHR CLAHRC NWL through previous participation in Quality Improvement Project Teams or the Fellowship, or through steering group meetings. This will include members of the NIHR CLAHRC NWL core team.
Group 4 will be individuals who are undertaking Quality Improvement work not supported or funded by NIHR CLAHRC NWL, but who are independently using some aspects of the CLAHRC NWL systematic approach or rolling out a project first developed with NIHR CLAHRC NWL.

All four groups will include NHS staff, Non-NHS Staff such as academic researchers and care home staff, and patients and members of the public. No patients will be recruited through their use of care services; rather, they will be recruited through their participation in the Quality Improvement networks under investigation (described as Group 1, Group 2, Group 3, and Group 4). These networks already include patients and members of the public; therefore these individuals will not be excluded from participation. Only the medical details which participants choose to

self-disclose will be part of the study, and researchers will not have access to any patient-identifiable medical records or clinical notes.

Group 1, Quality Improvement Project Teams: CLAHRC NWL works alongside project teams consisting of a clinical lead and a multidisciplinary group of individuals who will be responsible for and/or affected by an attempt to translate evidence into practice for healthcare improvement including patients and members of the public. One of the researchers named in this application will invite individuals to participate in interviews and/or focus groups through e-mail or work meetings, and if interested in participating, they will be sent an information sheet and consent form. We anticipate recruiting about 60 individuals from Group 1 to participate in interviews and/or focus groups. The leads of the project teams will also receive an information sheet regarding methods of documentary analysis and meeting observations, and will be invited to consent on behalf of their teams to these methods as described (see Documentary Analysis/ Meeting Observation Information Sheet and Documentary Analysis / Meeting Observation Consent Form).

Group 2, Individual Quality Improvement Fellowships: CLAHRC NWL provides training and mentoring for fellows who are each independently responsible for a Quality Improvement project. One of the researchers named in this application will invite individuals to participate in interviews and/or focus groups through e-mail or work meetings, and if interested in participating, they will be sent an information sheet and consent form. We anticipate recruiting 45 fellows to participate in interviews and/or focus groups. Fellows will also receive an information sheet regarding methods of documentary analysis and meeting observations, and will be given an opportunity to consent to analysis of documents they produce through their involvement in the fellowship.

Group 3, NIHR CLAHRC NWL Network: In addition to people who are actively engaged in CLAHRC NWL-supported Improvement Projects, we will also seek perspectives from the wider CLAHRC NWL network. This will include people who have previously been involved in projects funded and/or supported by CLAHRC NWL, members of CLAHRC NWL steering groups, and the CLAHRC NWL exchange network which is a multidisciplinary network enabling patients, carers, healthcare professionals and researchers to collaborate in Quality Improvement projects in

Healthcare. One of the researchers named in this application will invite individuals to participate in interviews and/or focus groups through e-mail and/or work meetings, and if interested in participating, they will be sent an information sheet and consent form. We anticipate recruiting about 60 individuals to participate in interviews and/or focus groups.

Group 4, Quality Improvement Network: The NHS patients, members of the public, NHS Staff, and Non-NHS Staff who are involved in Quality Improvement independent from NIHR CLAHRC NWL will be recruited through a self-selected sample of those who are, or have been, involved in quality improvement initiatives. They will be initially targeted through advertising the involvement opportunity on Twitter, through specific groups known to have carried out or been involved in quality improvement initiatives, such as the Kidney Alliance, organisations known to support improvement initiatives such as the Health Foundation, Healthcare Quality Improvement Partnership and posting an advert on the People in Research website. In addition, healthcare professionals and patients/public who have presented on their experiences in a quality improvement initiative at conferences, or written about their work in other arenas and whom have provided contact details on their slides, abstracts, papers, or relevant material, will be contacted by a researcher named in this application to gage their interest, send them the information sheet and asked to suggest others who may be interested in sharing their experiences. Active discussions take place on Twitter about quality improvement in the NHS and these will be monitored, and the opportunity will be highlighted to relevant individuals who will be asked to pass on the information to those who they feel are relevant. Potential participants will be contacted using a method that they prefer (e.g. this could be via Twitter, e mail, phone or letter). Expenses such as backfill for carers, childcare and/or travel costs will be provided to ensure we are less likely to discriminate against those who may not have the means to get involved. Formal interviews with these participants will be carried out after the receipt of a signed consent form. These interviews will be audiotaped, transcribed, anonymised and held in accordance with data protection. We anticipate recruiting approximately 140 individuals from this group to participate in interviews.

All participants (Groups 1-4): Potential participants will be approached by a researcher named in this application through the methods described above. This researcher will provide information about the study, why we want to talk to them, how we would keep and use the data, and that they are free to withdraw at any time. Informal conversations, led by researchers named in this application, will take place to give a brief introduction to the research and explain what their involvement could look like, as well as answer queries that may immediately arise. The information sheet will then be left with the potential participants, along with a consent form. The researcher will then follow up with potential participants a maximum of 3 times, no more often than once every 3 weeks. If the potential participant states that they do not want to be involved in the research at any time, communication will cease and any contact details held will be amended to state that the person should no longer be contacted to be involved. Participants may be asked to take part in up to 4 interviews, and/or up to 4 focus groups, due to the varied topics under investigation and the interest in longitudinal studies. Participants will be free to participate only in those interviews and/or focus groups which are of interest to them, and participants who have already declined participation will not be contacted again about interviews and/or focus groups. Interviews and/or focus groups will be conducted only after both the research and participant sign a copy of the consent form which will be kept on file in accordance with data protection. Participants will also be offered the opportunity for a consent form to be signed by both parties which can be kept for their own records.

All participants will also be invited to quarterly Collaborative Learning Events, bespoke training events, and access to online training tools supporting the use of the systematic approach. These training methods also provide forums for peer-to-peer support. Participants in these training methods will receive an anonymous survey to provide feedback on the training. The survey will specify that the results may be used for research purposes, and will give instructions on how to seek more information or to receive a participant information sheet.

Inclusion Criteria

- Play a role in a project team supported by NIHR CLAHRC NWL and/or participate in training, collaborative learning events, and/or steering groups, and/or involvement in a Quality Improvement project using some or all of the elements of the CLAHRC NWL systematic approach
- Speak English
- over 18 years old

Exclusion Criteria

- Not involved with CLAHRC NWL
- Not English-speaking
- Under 18 years old

Methodology

Data collection

Quality Improvement projects will be followed longitudinally over the course of project funding and for a follow up period of up to five years after the project ends, in order to assess long-term sustainment of improvement and value.

Each project consists of check points for more formal assessments – e.g. project reviews at 6, 12, and 18 months post-funding and monthly to quarterly use of the long term success tool.

These check points will consist of structured quantitative and qualitative information gathering and analysis. Teams will be assessed at the end of the project as to how effective teams were – this will involve analysis of data collected by teams, questionnaires, interviews and focus groups.

This longitudinal analysis will develop a narrative of the Quality Improvement journey and how the systematic approach influenced this both positively and negatively. We will perform quantitative and qualitative analysis of the extent to which use of systematic approach support success of project team.

Research will be conducted using the following methods:

Documentary analysis: In order to investigate engagement in Quality Improvement methodology and the systematic approach, as well as fidelity of use, researchers will analyse materials produced through routine business of applying the systematic approach to translate evidence into practice, for example minutes of team meetings, leaflets describing the improvement project, or diagrams depicting internal processes, procedures, and operations. These materials may also be used to investigate perspectives and contextual factors influencing the use of the systematic approach.

Observation of meetings: Researchers will observe facilitated workshops, working sessions, or routine meetings where Project Teams engage in training, peer-to-peer learning, or use the systematic approach to translate evidence into healthcare practice. This will enable investigation of engagement, facilitation and training in the systematic approach; fidelity of use of the systematic approach; individual perspectives and contextual factors.

Interviews: Interviews will be conducted using semi-structured interview method with open questions to allow participants to share their narratives about the process of applying the systematic approach to translating research into routine practice. This will enable investigation of engagement, facilitation and training in the systematic approach; outcomes of using the systematic approach; individual perspectives and contextual factors. Interviews will be recorded and transcribed and kept securely with access permitted only to approved researchers.

Questionnaires and surveys: Both anonymous and non-anonymous surveys will be conducted following workshops, training and collaborative learning events, and activities relating to elements of the systematic approach in order to gain a range of perspectives on the experience of using the systematic approach. This will enable investigation of engagement, facilitation and training in the systematic approach; individual perspectives and contextual factors. There will be two types of surveys which will be used and have been previously validated by this research group: One is a training experience survey, and the other is a survey about the use of elements of the systematic approach.

Storage of data: Each set of observations, interviews, and/or questionnaires must be part of a subproject which will go through an internal review of research protocol to ensure the standards set out in this ethics application are met. For any given sub-project, consent forms will be kept in a locked cabinet and any other participant-identifiable data will be stored on a secure password-protected drive, with access restricted to a limited number of researchers who either are identified in advance of data collection, or who do not have close working relationships (defined as direct line management, sharing work responsibilities, belonging to the same project team, and/or having weekly work interactions) with any of the participants. Personal data and research data will be retained for 10 years after completion of the study, after which point these will be destroyed, in line with the College Data Detention Policy. Consent: Informed consent will be obtained from fellows and clinical leads of project teams, who will sign a consent form containing information about the research project. Consent will include interview consent, and consent on behalf of the project team to use documents and observe meetings for research purposes.

Participants who receive surveys and questionnaires will be made aware that the information provided may be used for research.

All individuals who will be interviewed will sign a consent form containing information about the research project and who will have access to the data.

Data analysis

Factors influencing fidelity of use and outcomes of using the systematic approach:

Fidelity of use will be answered in part through analysis of documents. In instances where quality criteria exist for the assessment of Quality Improvement tool use fidelity (Taylor, McNicholas, Nicolay, Darzi, & Bell J., 2013), this will be used to evaluate the degree to which the Quality Improvement tool or aspect of the systematic approach was used as intended. Where no quality criteria exist, researchers will develop criteria from peer-reviewed literature providing guidance on the use of the methods and the theoretical benefits of their use.

Researchers will conduct semi-structured interviews with people who have used some or all components of the systematic approach or who have received care in the systems in which the Quality Improvement projects intervened. Participants will be encouraged to share their perspectives on the use of the systematic approach, outcomes of the project, and the factors which influenced these aspects. Interview transcripts will be interpreted using both deductive thematic analysis and theory-driven inductive thematic analysis.

Engagement, facilitation, and training in methods and tools in the systematic approach:

Effectiveness of training will be measured at different levels using the Kirkpatrick Model and Bloom's Taxonomy as a theoretical basis (Bloom, 1956; Kirkpatrick, 1979). In the Kirkpatrick model, there are several levels at which training can be considered successful. Level 1: reaction (to what extent did participants react favourably to the training), Level 2: learning (to what extent did participants learn the concepts presented in training), and intentions for Level 3: behaviour (to what extent did participants change their behaviour as a result of training) will be measured through post-training questionnaires and surveys.

Kirkpatrick Model Level 3: Behaviour and Level 4: Outcomes (to what extent were healthcare improvement outcomes achieved as a result of the training) will be investigated through focus groups and interviews, particularly in the follow-up stage after projects have completed.

Engagement in training will be analysed according to quantitative analysis of proportions of project team members who attend training events and/or use training materials. Reasons for engagement or disengagement will be investigated through meeting observations, interviews, and focus groups.

Data will also be analysed according to Bloom's Taxonomy, which proposes several levels in which learning can be obtained: remembering, understanding, applying, analysing, evaluating, and creating.

Exploration of contextual factors and perspectives of groups and individuals in the evidence translation process:

Data about the context of quality improvement and perspectives of groups and individuals will be collected through participant and non-participant observation of meetings and workshops, interviews, and focus groups.

From these interviews, focus groups, and observations, three forms of analysis will be utilised.

1. Telling their stories

At a simple level the narratives will be utilised to create narratives highlighting the value and limitations of how different contributions can support improvement in healthcare.

2. Mapping contributions

As well as 'telling their stories' the data will be analysed and mapped against the theoretical framework – with the aim of demonstrating the breadth of different contributions which need to be considered in improving health and to start considering how they fit together, the overlaps, the gaps, the contradictions that affect collaborative experimental learning to improve healthcare.

3. Thematic analysis

In addition to descriptive analysis thematic analysis will be used to explore how individuals construct the value and limitations of their contributions within the context and structures they work within. The aim of this analysis will be to identify success factors and frustrations experienced and to identify and where possible explore underlying assumptions which influence or are influenced by collaborative working. The longitudinal nature of data collection will enable individuals perceptions and experiences to be tracked over a limited period of time and to better understand the 'shifting perceptions' of how value is constructed and reconstructed over time.

Regulatory Issues

Ethics Approval

The study has been approved by Imperial College (as study sponsor), Imperial College NHS Trust, Chelsea and Westminster NHS Trust, and the HRA (ref SL-AR3). The study will be conducted in accordance with the recommendations for

physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Ethical considerations

Situation: involvement of researchers as participants

Summary: NIHR CLAHRC NWL funds and supports Quality Improvement Teams consisting of multidisciplinary staff (such as managers, doctors, nurses, pharmacists, and physiotherapists) and patients to use the systematic approach in projects lasting a fixed term e.g. 12 or 18 months. The research in this study utilizes an 'action research' methodology which is designed as an iterative process of action, reflection, and improvement, with the ultimate purpose of developing a systematic way to enable improvement. This means researchers will support Quality Improvement projects by communicating their findings with projects at short intervals and may be involved in close working relationships with these teams. For example, a researcher investigating the use of the Long-Term Success tool in one team may then use those findings to deliver training to other teams. The way that training is delivered to project teams is another line of investigation in this research; thus the researcher for one project may be a research participant for another project.

Ethical consideration: Multiple researchers would be able to utilise the data collected from observations, interviews, and documentary analysis, to explore the research questions posed in this study from different perspectives and through different examples; however, because some of these researchers may also be participants, or may have close working relationships with some of the research participants, it would not be appropriate for every researcher to have access to the entire dataset.

How this will be addressed: We will establish internal governance procedures by which researchers involved in this project will specify how their sub-project will comply with the programme-level ethics to ensure confidentiality of records. The data being collected in the interviews, focus groups, and observations of meetings and workshops will be stored securely on Imperial College servers (password protected access and backed up daily), with access provided only to researchers who have been approved to access that sub-project's data, to protect the identity of the individuals involved and to encourage them to share honestly their experiences,

reflections and feelings. A log of researchers engaged with the study and with permission to access files will be kept by the research portfolio coordinator and PI and academic lead.

Situation: Involvement of patients and members of the public as research participants

Summary: This study will explore their engagement of both healthcare professionals and patients and public members in the conduct of quality improvement and evidence translation efforts. For example, if a Quality Improvement project is using the systematic approach to improve the provision of water to care home residents, the family member of one of the residents may act as a professional lay member of the Quality Improvement Team that uses the systematic approach to improve care. Thus, this team member may be recruited for observations of workshops and meetings of the Quality Improvement Team or interviewed about aspects of the systematic approach. There may also be patients who have received care previously, or may be recipients of care in the future, that directly relates to the area of care being improved. For example a patient who has previously had cancer surgery, or is scheduled to have cancer surgery, may be recruited to a Quality Improvement Team or involved in focus groups to understand their experiences and gain their input to future improvement efforts.

Ethical considerations: When patients are involved in research, it is important to clarify whether there are any clinical interventions or deviations from the standard care that patients would typically receive if they were not participating in research. The research study in question will not involve any clinical interventions, and patients can expect to receive the same care regardless of whether they choose to participate in the research study or the Quality Improvement project. It is important that patients and members of the public are made fully aware of this distinction, and clearly understand the purpose of the research and that participation is fully voluntary.

How this will be addressed: Members of the public will only be involved so much as they play a role within the existing networks of the organizations under study. Participants will be recruited via existing voluntary contact with the research investigators, clinical leads, or fellows leading each Quality Improvement project, or

by having presented their involvement in a Quality Improvement project in a public forum. Like all participants in this research, those patients and members of the public who are recruited to interviews and/or focus groups will receive an information sheet about the study in lay-friendly language, which clearly states that participation is optional and that they can expect to receive the same standard care regardless of their decision to participate or not participate in research. All interviewees and focus group participants being recorded will be asked to complete an informed consent form and will be able to withdraw from the study at any point.

Situation: Confidentiality of information and informed consent.

Summary: Interviews, focus groups, and meeting observations may uncover issues which participants would not want to be shared widely, particularly with people with whom they have close working relationships.

Ethical considerations: The interviews and workshops are not anticipated to be highly sensitive but issues discussed could link to emotions relating to frustration, feelings of failure or low self value. Research participants must also be aware that the documents produced by project teams and views expressed in meetings, interviews, surveys, and focus groups may be used for research purposes.

How this will be addressed: Participants in interviews and focus groups will receive information sheets about the study and sign consent forms. Clinical leads and fellowship leads for each project will be informed that documents produced by the team and meetings may be observed and analysed for research purposes. Project leads will sign acknowledgement of their responsibility for communicating this to their team members. Identifiable information will be accessible only by researchers approved for the subproject. Names and identifying features will be removed from transcripts and observation notes for the purposes of publication and dissemination. Researchers will take care to deal with any emergent issues of feelings of failure or low self-value sensitively and if necessary would direct participants to relevant support services.

Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. All recorded and transcribed information will be stored securely on Imperial College servers (password protected access and backed up daily). Access will only be permitted to this information by the study PI and approved researchers. A log of researchers engaged with the study and with permission to access files will be kept by the PI.

Data reported for dissemination will remove all identifiable factors (e.g. names, organisations) and replace them with pseudo-identifiable names e.g. Interviewee A; Organisation 1. In the case of any serious misconduct/malpractice being revealed during the study issues will be discussed with an individual's line manager and if necessary escalated through appropriate Trust or University procedures.

Adverse Events

It is not expected that any adverse events will occur during the study, but any problems will be discussed with the head of department and the Joint Research Compliance Office.

Outputs and dissemination

We expect this work will lead to the refinement of the CLAHRC NWL systematic approach for translating evidence into practice, which will be transferrable across the NHS and provide generalised learning for healthcare organisations internationally. This will include theoretical outputs articulating the approach based on previous peer-reviewed literature, and will also include pragmatic outputs designed to help individuals to understand not just *what* needs to happen for evidence translation, but *how* to overcome the common pitfalls to translate evidence into lasting improvements in healthcare.

CLAHRC NWL will promote dissemination through traditional academic channels including peer reviewed journals and conferences, as well as continuing to publish in more widely accessed magazines such as HSJ, Nursing Times and Junior Doctors. Dissemination will also be achieved through joint working initiatives with other

CLAHRC programmes who are similarly funded to accelerate the uptake of research into practice (e.g. knowledge exchange model with South Yorkshire CLAHRC), as well as through annual reports to our funding agencies (NIHR and Health Foundation).

CLAHRC NWL also recognises the role that patients and members of the public play as change agents, as exemplified 'My Medication Passport' and the development of apps for self-management of asthma and sickle cell disease. Building on our experience we will use social media forums including Twitter and virtual worlds to access a broader group of stakeholders including accessing feedback on the CLAHRC NWL programme.

In addition, members of the CLAHRC NWL External Advisory Group have a role as "CLAHRC NWL Champions" and we anticipate that this group of national and international leaders in healthcare, research, industry and other fields will further facilitate dissemination and help to build our standing as a national resource to support such work.

Publication Policy

Investigators will endeavour to publish all results in peer-reviewed academic journals. Wherever possible investigators will publish open-access papers.

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APPENDIX D PERMISSION LETTER TO REPRODUCE AN EXTRACT FROM A THIRD PARTY'S WORK

01/06/2019

Dear Dr Laura Lennox,

I am completing my PhD thesis at Imperial College London entitled 'Is comprehensive medication review cost effective for patients admitted to hospital?'

I seek your permission to reprint, in my thesis an extract from: Lennox, L., Stillman, N., Barber, S., & Reed, J. E. (2019). From theory to practice: considering the spread of health care improvement through a medication review initiative. The extract to be reproduced is: Figure 4 Intervention components of the ReMAC initiative.

I would like to include the extract in my thesis which will be added to Spiral, Imperial's institutional repository http://spiral.imperial.ac.uk/ and made available to the public under a Creative Commons Attribution Non Commercial 4.0 International Licence (CC BY-NC).

If you are happy to grant me all the permissions requested, please return a signed copy of this letter. If you wish to grant only some of the permissions requested, please list these and then sign.

Yours sincerely,

Tomasz Szymanski

Imperial College London, Department of Medicine

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Name: LAURA LENNOX

Organisation: ARC NWL, IMPERIAL COLLEGE LONDON.

Job title: RESEARCH ASSOCIATE